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<p>(21) International Application Number: PCT/US97/22519 (22) International Filing Date: 18 December 1997 (18.12.97) (30) Priority Data: 08/771,714 20 December 1996 (20.12.96) US (71) Applicant: SCHERING CORPORATION [US/US]; 2000 Gal- loping Hill Road, Kenilworth, NJ 07033 (US). (72) Inventor: McCORMICK, Kevin, D.; 5 Pace Drive, Edison, NJ 08820 (US). (74) Agents: MAGATTI, Anita, W. et al.; Schering-Plough Cor- poration, Patent Dept., K-6-1 1990, 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US).</p>		<p>(81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CZ, EE, GE, GW, HU, ID, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
<p>(54) Title: SPIRO-SUBSTITUTED AZACYCLIC-SUBSTITUTED PIPERAZINO DERIVATIVES AS NEUROKININ ANTAGONISTS</p>		
<p>(57) Abstract</p> <p>The invention relates to compounds of formula (I), wherein Z, R_c, y, m, u, Ar₁, n, X, R_{c'}, I and Ar₂ are as described herein. These compounds are neurokinin antagonists. These compounds are useful in the treatment of chronic airway diseases such as asthma.</p> <div style="text-align: center;"> <p>(I)</p> </div>		

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**SPIRO-SUBSTITUTED AZACYCLIC-SUBSTITUTED
PIPERAZINO DERIVATIVES AS NEUROKININ ANTAGONISTS**

BACKGROUND OF THE INVENTION

10 The present invention relates to a genus of compounds
useful as antagonists of neurokinin receptors. In particular, these can be
neurokinin-1 receptor (NK₁) antagonists. Some can also be neurokinin-
1 receptor (NK₁) antagonists and neurokinin-2 receptor (NK₂)
antagonists, that is, NK₁ / NK₂ dual receptor antagonists. Some can also
15 be neurokinin-2 receptor (NK₂) antagonists. Some can also be
neurokinin-3 receptor (NK₃) antagonists.

 Neurokinin receptors are found in the nervous system and
the circulatory system and peripheral tissues of mammals, and therefore
are involved in a variety of biological processes. Neurokinin receptor
20 antagonists are consequently expected to be useful in the treatment or
prevention of various mammalian disease states, for example
pulmonary disorders like asthma, cough, bronchospasm, chronic
obstructive pulmonary diseases, and airway hyperreactivity; skin
disorders and itch, for example, atopic dermatitis, and cutaneous wheal
25 and flare; neurogenic inflammatory diseases such as
arthritis, migraine, nociception; CNS diseases such as anxiety, emesis,
Parkinson's disease, movement disorders and psychosis; convulsive
disorders, renal disorders, urinary incontinence, ocular inflammation,
inflammatory pain, and eating disorders such as food intake inhibition;
30 allergic rhinitis, neurodegenerative disorders, psoriasis, Huntington's
disease, depression, and various gastrointestinal disorders such as
Crohn's disease.

 In particular, NK₁ receptors have been reported to be
involved in microvascular leakage and mucus secretion, and NK₂
35 receptors have been associated with smooth muscle contraction,

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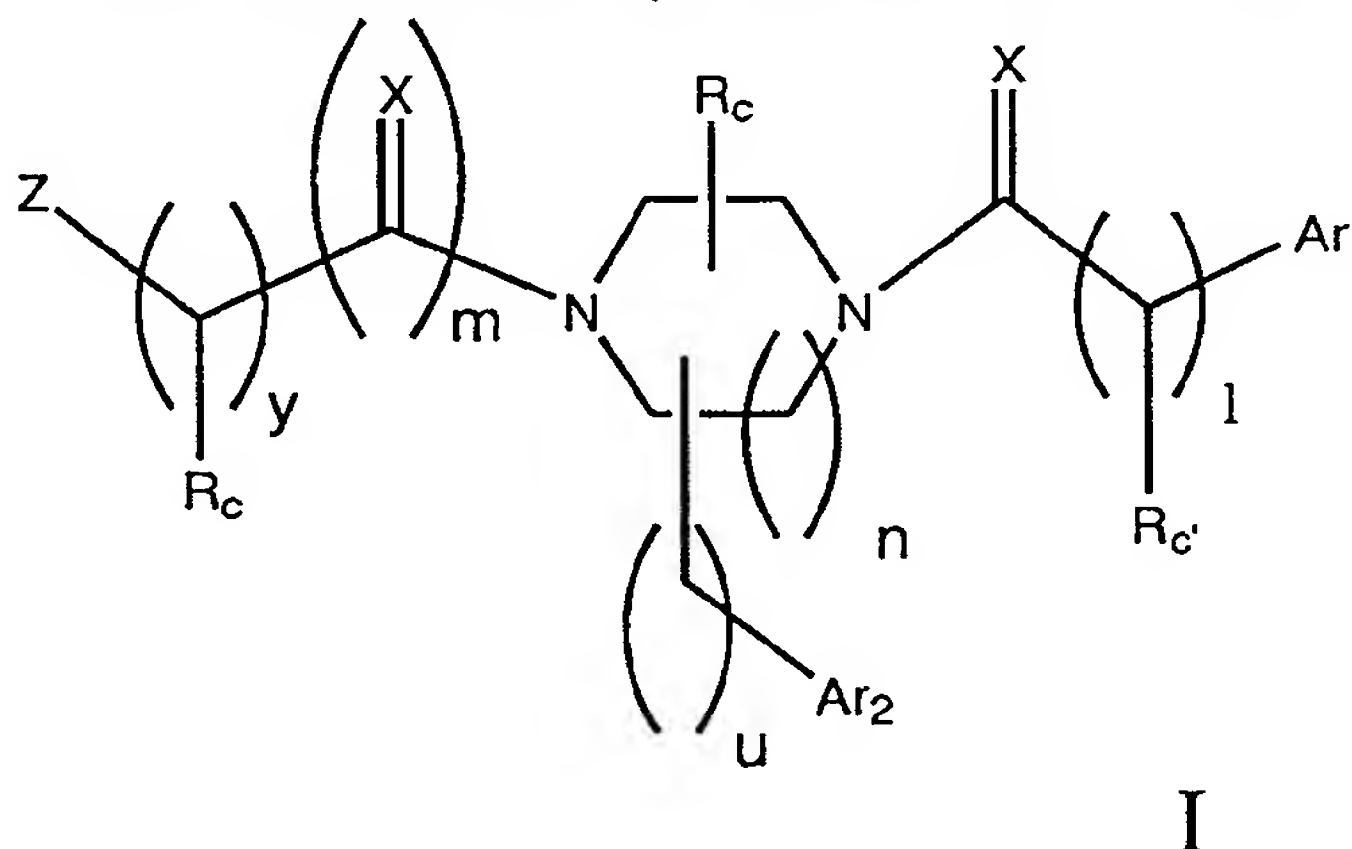
making NK₁ and NK₂ receptor antagonists especially useful in the treatment and prevention of asthma.

Moreover, NK₃ receptor antagonists are especially useful in the treatment and prevention of asthma, inflammatory diseases and conditions, such as ocular inflammation, allergic rhinitis, cutaneous wheal and flare, psoriasis, atopic dermatitis, CNS diseases such as anxiety and Parkinson's disease.

Spiro-substituted azacyclic NK₁ and NK₂ receptor antagonists have been disclosed in WO 94/29309, published December 22, 1994, and in WO 94/17045, published August 4, 1994. Piperazino NK₁ and NK₂ receptor antagonists have been disclosed in WO 96/34864, published November 7, 1996.

SUMMARY OF THE INVENTION

The invention relates to compounds of the formula:



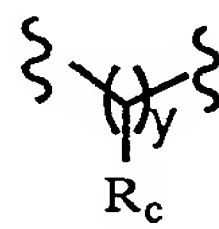
wherein

each X is independently selected from the group consisting of =O, (H,H), =NR_d, and =S;

n is 0 to 2; u is 0 to 2; l is 0 to 2;

m is 1, and y is 1 to 3; or m is 2, and y is 0;

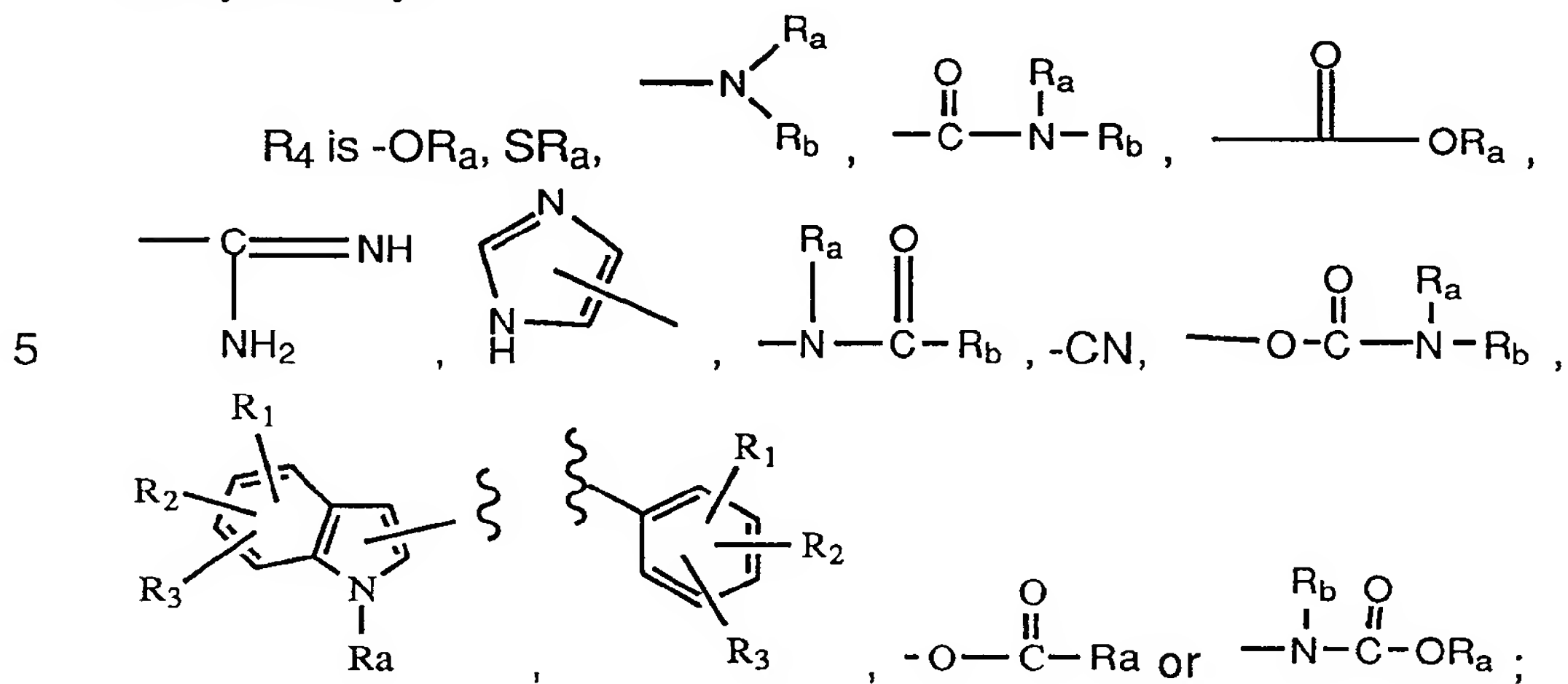
each R_c is independently selected from the group consisting of H, C₁-C₆ alkyl and -(CH₂)_{n1}-R₄, wherein n₁ is 1 to 6, with the proviso that



no more than one R_c is other than H in the moiety;

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R_d is independently selected from the group consisting of H, C₁-C₆ alkyl, -CN, -OR_a, phenyl, substituted phenyl, benzyl, substituted benzyl, or allyl;



$R_{c'}$ is H, C₁-C₆ alkyl or (CH₂)_nOR_a, with the proviso that no more than one $R_{c'}$ is other than H;

10 each R_a and R_b is independently selected from the group consisting of H, C₁-C₆ alkyl, phenyl, substituted phenyl, benzyl, substituted benzyl and allyl; with the proviso that when R_4 is

$\text{---N} \begin{smallmatrix} R_b \\ | \\ \text{C(=O)---OR}_a \end{smallmatrix}$, R_a is not H; or when R_a and R_b are attached to the same nitrogen, then R_a and R_b , together with the nitrogen to which they are attached, can form a 4 to 7 member ring;

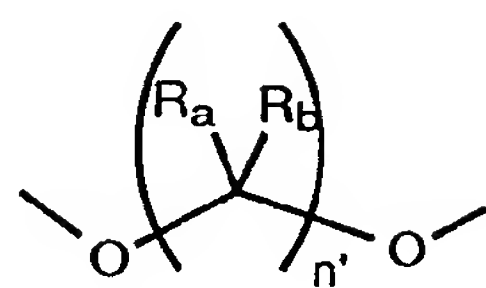
15 each R_1 and R_2 is independently selected from the group consisting of H, C₁-C₆ alkyl, -CF₃, -C₂F₅, Cl, Br, I, F, -NO₂, -OR_a, -CN,

$\text{---NR}_a\text{R}_b$, ---C(=O)Ra , ---O-C(=O)Ra , $\text{---O-C(=O)N} \begin{smallmatrix} R_a \\ R_b \end{smallmatrix}$, $\text{---N} \begin{smallmatrix} R_b \\ | \\ \text{C(=O)---OR}_a \end{smallmatrix}$, $\text{---N} \begin{smallmatrix} R_a \\ | \\ \text{C(=O)---R}_b \end{smallmatrix}$, ---C(=O)OR_a , $\text{---C(=O)N} \begin{smallmatrix} R_a \\ R_b \end{smallmatrix}$, ---S---Ra , ---S(=O)---Ra , -SR_a, and ---S(=O)---NHR_a ; provided R_a is not H in ---S---Ra , ---S(=O)---Ra , or

20 $\text{---N} \begin{smallmatrix} R_b \\ | \\ \text{C(=O)---OR}_a \end{smallmatrix}$;

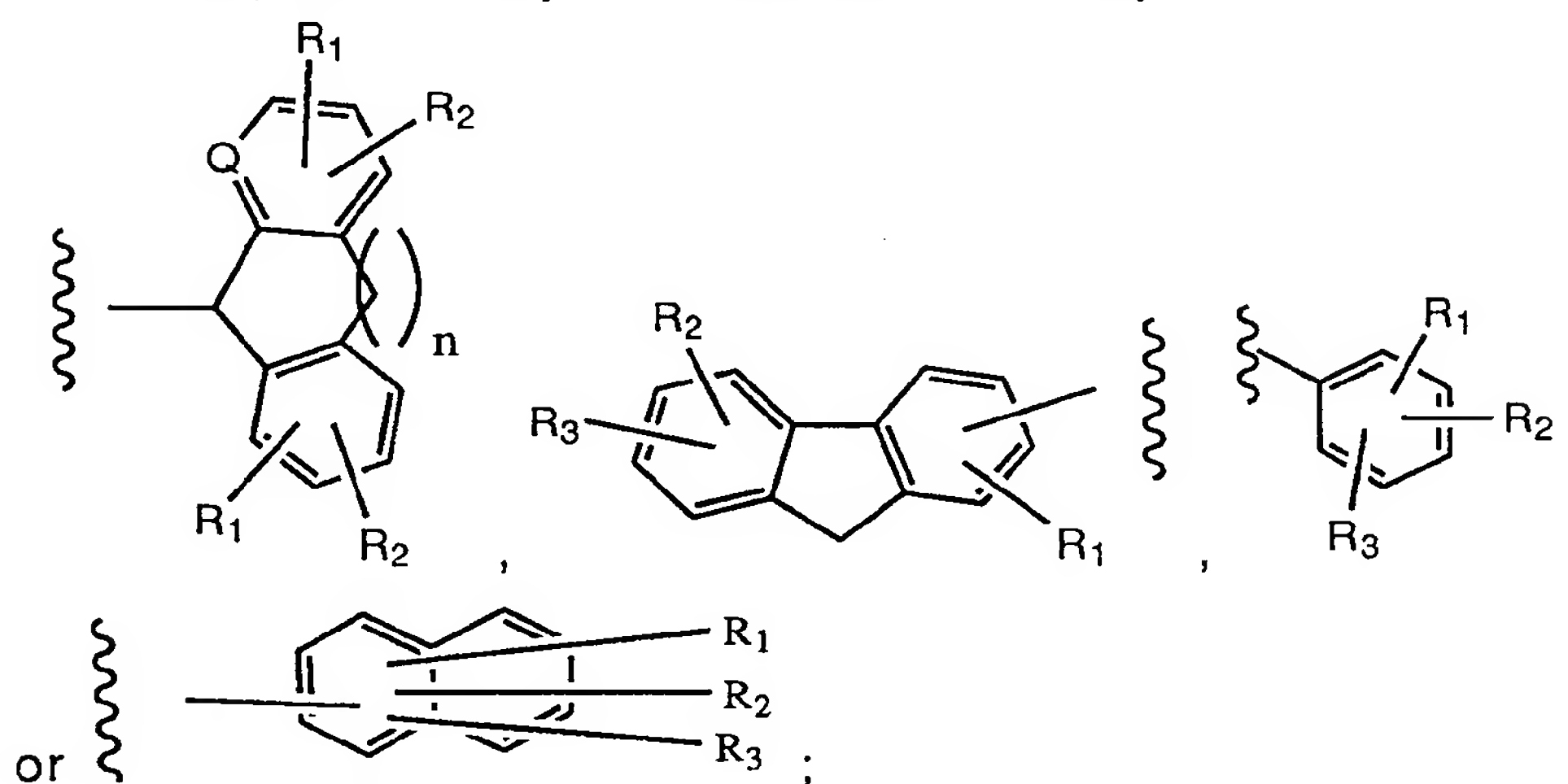
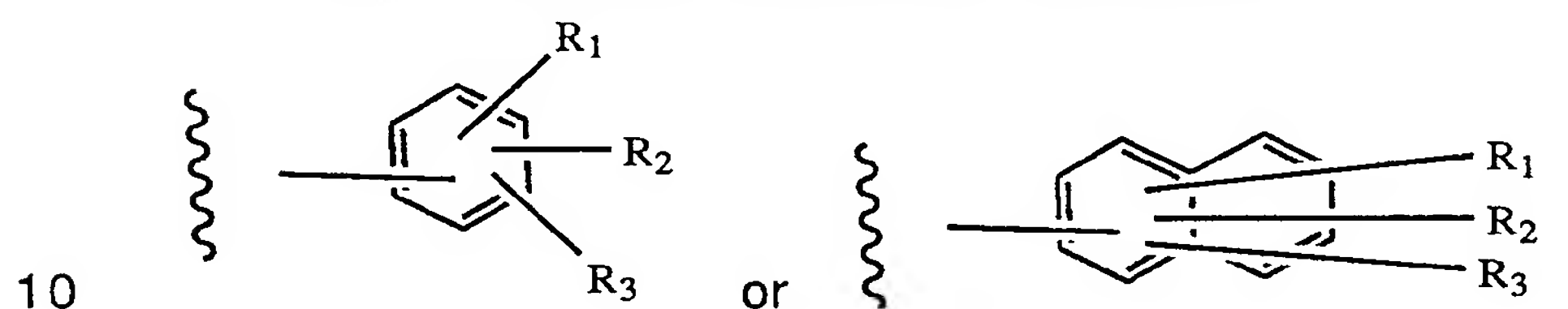
or when R_1 and R_2 are on adjacent carbons on a ring, they can form

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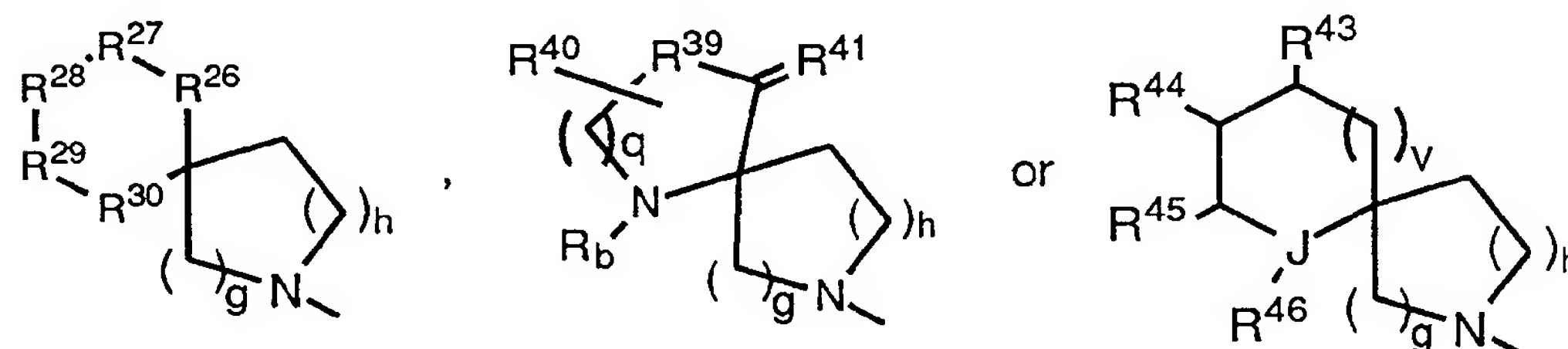
wherein n' is 1 or 2;each R_3 is independently selected from the group consisting of H,

C_1 - C_6 alkyl, $-CF_3$, $-C_2F_5$, $-\overset{\overset{O}{\parallel}}{C}-R_a$, $-O-\overset{\overset{O}{\parallel}}{C}-R_a$, $-\overset{\overset{O}{\parallel}}{C}-N(R_a)-R_b$, Cl, Br, I, F, $-OR_a$, $-OCF_3$ or phenyl;

5

 Ar_1 is heteroaryl or substituted heteroaryl, Q is $=N-$ or $=CH-$; Ar_2 is heteroaryl, substituted heteroaryl,

10

 Z is

wherein the nitrogen in the unsubstituted ring is optionally quaternized with C_1 -4 alkyl or phenyl- C_1 -4 alkyl or is optionally present as the Noxide (N^+O^-);

15

- 5 -

g and h are each independently 0, 1, 2, 3, 4, or 5, with the proviso that g + h is equal to 1, 2, 3, 4, or 5;

v is 0, 1 or 2;

R²⁶ is selected from the group consisting of

- 5 (1) a covalent bond
- (2) C₁₋₃ alkylene, unsubstituted or substituted with a substituent selected from the group consisting of =O, -OH, -OR³⁵, halogeno, -CF₃, phenyl or mono, di or trisubstituted phenyl, wherein the substituents on the phenyl are independently selected from -OH, -CN,
- 10 halogeno and -CF₃,
- (3) S(O)_k
- (4) (C₁₋₃ alkylene)-S(O)_k
- (5) S(O)_k-(C₁₋₂ alkylene)
- (6) S(O)_kNH
- 15 (7) S(O)_j-NR³⁵
- (8) S(O)_j-NR³⁵-(C₁₋₂ alkylene)
- (9) CONH
- (10) CONR³⁵-(C₁₋₂ alkylene)
- (11) CO₂ and
- 20 (12) CO₂-(C₁₋₂ alkylene)

wherein j is 1 or 2 and k is 0, 1 or 2;

R²⁷ is -NR³⁷-, -O-, -S-, -S(O)-, or -SO₂-, with the proviso that when R²⁶ is a covalent bond and R²⁸ is C₁₋₃ alkyl, R²⁷ must be NR³⁷;

R³⁷ is selected from a group consisting of:

- 25 (1) H,
- (2) C₁₋₈ linear or branched alkyl, unsubstituted, monosubstituted or multiply substituted with -OR³⁵, =O, -NHCOR³⁵, -NR³⁵R³⁶, -CN, -halogeno, -CF₃, -phenyl or substituted phenyl, wherein the substituents on phenyl are selected from the group consisting of
- 30 -OH, -CN, halogeno and -CF₃;
- (3) S(O)R³⁸, wherein R³⁸ is C₁₋₆ linear or branched alkyl, unsubstituted, mono di or trisubstituted with a substituent selected from the group consisting of =O, -CN, -OR³⁵, -NR³⁵R³⁶, -NR³⁶OR³⁶, -halogeno, -CF₃, -phenyl or mono, di or trisubstituted phenyl, wherein the
- 35 substituents on the phenyl are independently selected from the group

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consisting of -OH, =O, -CN, -NR³⁵R³⁶, -NR³⁵COR³⁶, -halogeno, -CF₃ and C₁₋₃ alkyl;

- 5 (4) SO₂R³⁸,
 (5) COR³⁸,
 (6) CO₂R³⁸;
 (7) CONR³⁶R³⁸;

R²⁸ is selected from the group consisting of

- (1) a covalent bond
 (2) C₁₋₃ alkylene, unsubstituted or substituted with a
 10 substituent selected from the group consisting of =O, -OR³⁵, halogeno, -CF₃, phenyl or mono, di or trisubstituted phenyl, wherein the substituents on the phenyl are independently selected from the group consisting of -OR³⁵, halogeno and -CF₃;

- (3) S(O)_k
 15 (4) (C₁₋₃ alkylene)-S(O)_k
 (5) S(O)_k-(C₁₋₂ alkylene)
 (6) NHS(O)_j
 (7) NH(C₁₋₂ alkylene)-S(O)_j
 (8) S(O)_jNR³⁵
 20 (9) S(O)_j-NR³⁵-(C₁₋₂ alkylene)
 (10) NHCO-(C₁₋₂ alkylene)
 (11) NR³⁵CO
 (12) NR³⁵-(C₁₋₂ alkylene)-CO
 (13) O(CO) and
 25 (14) (C₁₋₂ alkyl)O(CO);

R²⁹-R³⁰ considered together are 2 adjoining atoms of the ring



said ring being a phenyl, naphthyl or heteroaryl group, and wherein the phenyl, naphthyl or heteroaryl group is unsubstituted, mono, di or tri substituted, wherein heteroaryl is selected from the group consisting of benzimidazolyl, benzofuranyl, benzoxazolyl, furanyl, imidazolyl, indolyl, isoxazolyl, isothiazolyl, oxadiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridyl, pyrimidyl, pyrrolyl, quinolyl, tetrazolyl, thiadiazolyl, thiazolyl, thienyl and triazolyl; and wherein the substituents
 30 are independently selected from the group consisting of:
 35

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- (a) C₁₋₆ alkyl, branched or unbranched, unsubstituted or mono or disubstituted by hydroxy
- (b) =O
- (c) OR³⁵
- 5 (d) halogeno
- (e) CF₃
- (f) NO₂
- (g) CN
- (h) NR³⁵R³⁶
- 10 (i) NR³⁵COR³⁶
- (j) NR³⁵CO₂R³⁶
- (k) NR³⁵S(O)_jR³⁶
- (l) CONR³⁵R³⁶
- (m) COR³⁵
- 15 (n) CO₂R³⁵
- (o) S(O)_jR³⁵
- (p) heteroaryl, or mono or di substituted heteroaryl,
- wherein heteroaryl is as defined above and the substituents are selected from the group consisting of: C₁₋₆ alkyl, branched or
- 20 unbranched, unsubstituted or mono or disubstituted by OH; =O; OR³⁵; CF₃; -NO₂; CN; NR³⁵R³⁶; NR³⁵COR³⁶; NR³⁵CO₂R³⁶; NR³⁵S(O)_jR³⁶; CONR³⁵R³⁶; COR³⁵; CO₂R³⁵; S(O)_jR³⁵; and phenyl;
- R³⁵ and R³⁶ are independently selected from:
- (a) H,
- 25 (b) C₁₋₆ alkyl, or mono or disubstituted C₁₋₆ alkyl, wherein the substituents independently selected from the group consisting of phenyl, unsubstituted or substituted with -OH, C₁₋₃ alkyl, -CN, halogeno, -CF₃ or C₁₋₄ alkoxy; -OH; =O; -CN; halogeno; or -CF₃;
- (c) phenyl, pyridinyl or thiophene, or mono, di or
- 30 trisubstituted phenyl, pyridinyl or thiophene, wherein the substituents are independently selected from the group consisting of -OH, C₁₋₄ alkyl, -CN, halogeno and -CF₃;
- (d) C₁₋₃ alkyloxy,
- or
- 35 R³⁵ and R³⁶ are joined together to form a 5-, 6-, or 7-membered monocyclic saturated ring containing 1 or 2 heteroatoms

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independently selected from nitrogen, oxygen, and sulfur, and in which the ring is unsubstituted or mono or disubstituted, wherein the substituents are independently selected from the group consisting of -OH, =O, -CN, halogeno and -CF₃;

5 q is 1 or 2;

 R³⁹ is -NR_b- or -CH₂-;

 R⁴⁰ is H, C₁-C₆ alkyl, =O, phenyl, substituted phenyl, benzyl, substituted benzyl or allyl;

 R⁴¹ is =O or =S;

10 J is carbon and R⁴³, R⁴⁴, R⁴⁵ and R⁴⁶ are independently selected from the group consisting of H, -OH, =O, -NR⁴⁷R⁴⁸ or -NR⁴⁷C(O)-NR⁴⁷R⁴⁸, wherein the nitrogen of -NR⁴⁷R⁴⁸ is optionally quaternized with C₁-4 alkyl or phenyl-C₁-4 alkyl or is optionally present as the N-oxide; or R⁴³ and R⁴⁴, or R⁴⁴ and R⁴⁵, together form a carbon-carbon bond; or R⁴³ and R⁴⁴ or R⁴⁴ and R⁴⁵, or R⁴⁵ and R⁴⁶, together with the
15 carbons to which they are attached form an aryl or heteroaryl ring, wherein heteroaryl is as defined above, and wherein the aryl or heteroaryl group is unsubstituted, mono, di or tri substituted, wherein the substituents are independently selected from the group consisting of:

20 (a) C₁-6 alkyl, branched or unbranched, unsubstituted or mono or disubstituted by hydroxy

 (b) =O

 (c) OR⁴⁷

 (d) halogeno

25 (e) CF₃

 (f) NO₂

 (g) CN

 (h) NR⁴⁷R⁴⁸

 (i) NR⁴⁷COR⁴⁸

30 (j) NR⁴⁷CO₂R⁴⁸

 (k) NR⁴⁷S(O)_jR⁴⁸

 (l) CONR⁴⁷R⁴⁸

 (m) COR⁴⁷

 (n) CO₂R⁴⁷

35 (o) S(O)_kR⁴⁷

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- (p) heteroaryl, or mono or di substituted heteroaryl, wherein heteroaryl is as defined above and the substituents are selected from the group consisting of: C₁₋₆ alkyl, branched or unbranched, unsubstituted or mono or disubstituted by OH; =O; OR⁴⁷; CF₃; -NO₂; CN; NR⁴⁷R⁴⁸; NR⁴⁷COR⁴⁸; NR⁴⁷CO₂R⁴⁸; NR⁴⁷S(O)_jR⁴⁸; CONR⁴⁷R⁴⁸; COR⁴⁷; CO₂R⁴⁷; S(O)_jR⁴⁷; and phenyl;
- 5 or R⁴³, R⁴⁴ and R⁴⁵ are as defined above and J-R⁴⁶ is oxygen or S(O)_i, wherein i is 0, 1, or 2; and
- R⁴⁷, R^{47'} and R⁴⁸ are independently selected from the group
- 10 consisting of:
- (a) H,
- (b) C₁₋₆ alkyl, or mono or disubstituted C₁₋₆ alkyl, wherein the substituents independently selected from the group consisting of phenyl, -OH, =O, -CN, halogeno and -CF₃;
- 15 (c) phenyl, naphthyl, or mono, di or trisubstituted phenyl or naphthyl, wherein the substituents are independently selected from the group consisting of -OH, C₁₋₃ alkyl, -CN, halogeno and -CF₃; and
- (d) C₁₋₃ alkyloxy; or
- R⁴⁷ and R⁴⁸ are joined together to form a 5-, 6-, or 7-
- 20 membered monocyclic saturated ring containing 1 or 2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and in which the ring is unsubstituted or mono or disubstituted, wherein the substituents are independently selected from the group consisting of -OH, =O, -CN, halogeno and -CF₃;
- 25 or any enantiomer or diastereomer thereof,
- or a pharmaceutically acceptable salt thereof.

All of the variables in the above formulas such as Z, R₁, R₂, and R₃, have the same meaning throughout the specification unless

30 otherwise specified.

Preferred compounds of the invention are compounds of formula I wherein each X is =O or (H,H) and at least one X is =O.

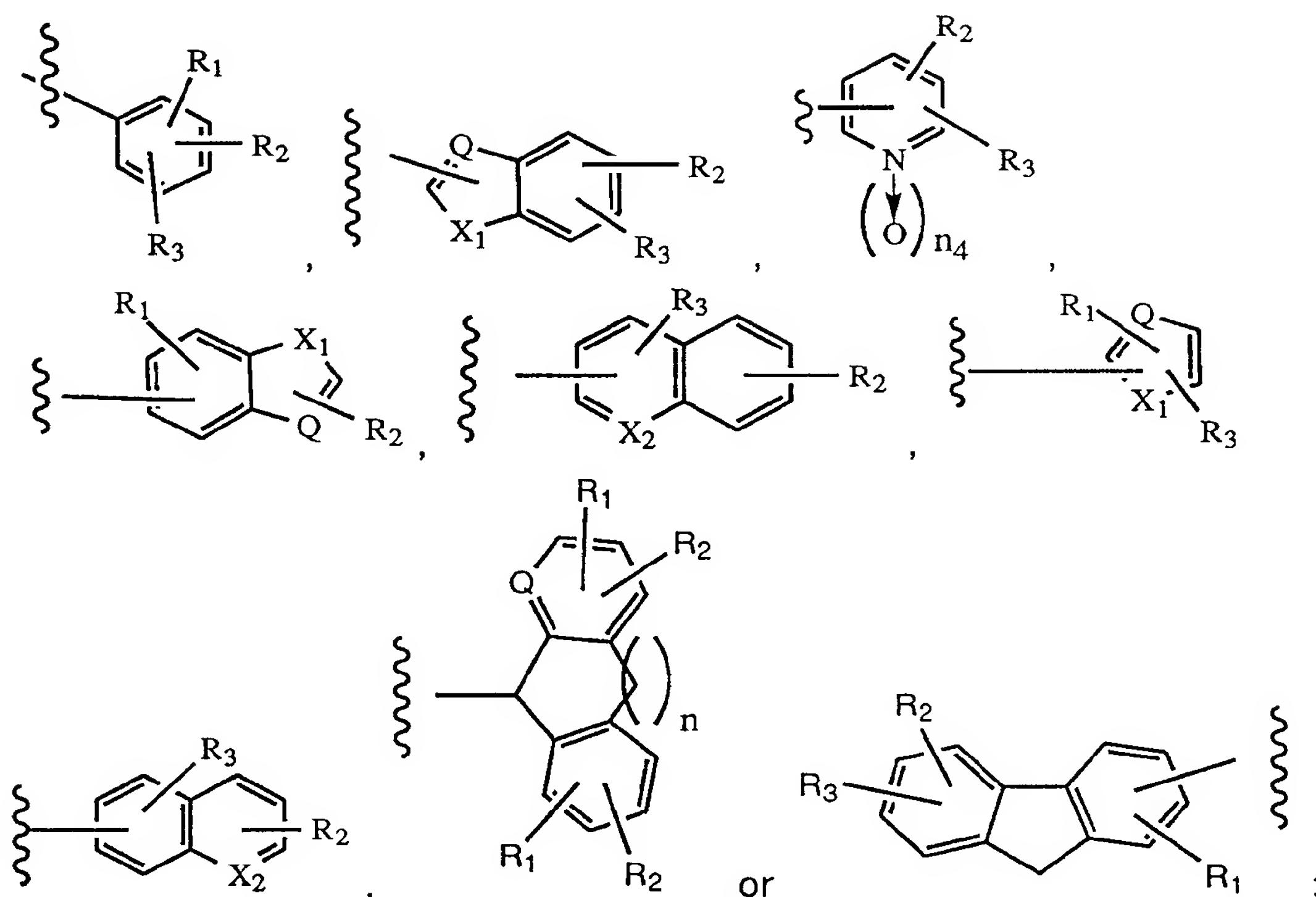
Also preferred are compounds of formula I wherein each X is =O.

Also preferred are compounds of formula I wherein l is 0, m is 1, n

35 is 1, u is 0 and y is 1-3.

Also preferred are compounds of formula I wherein Ar₁ is

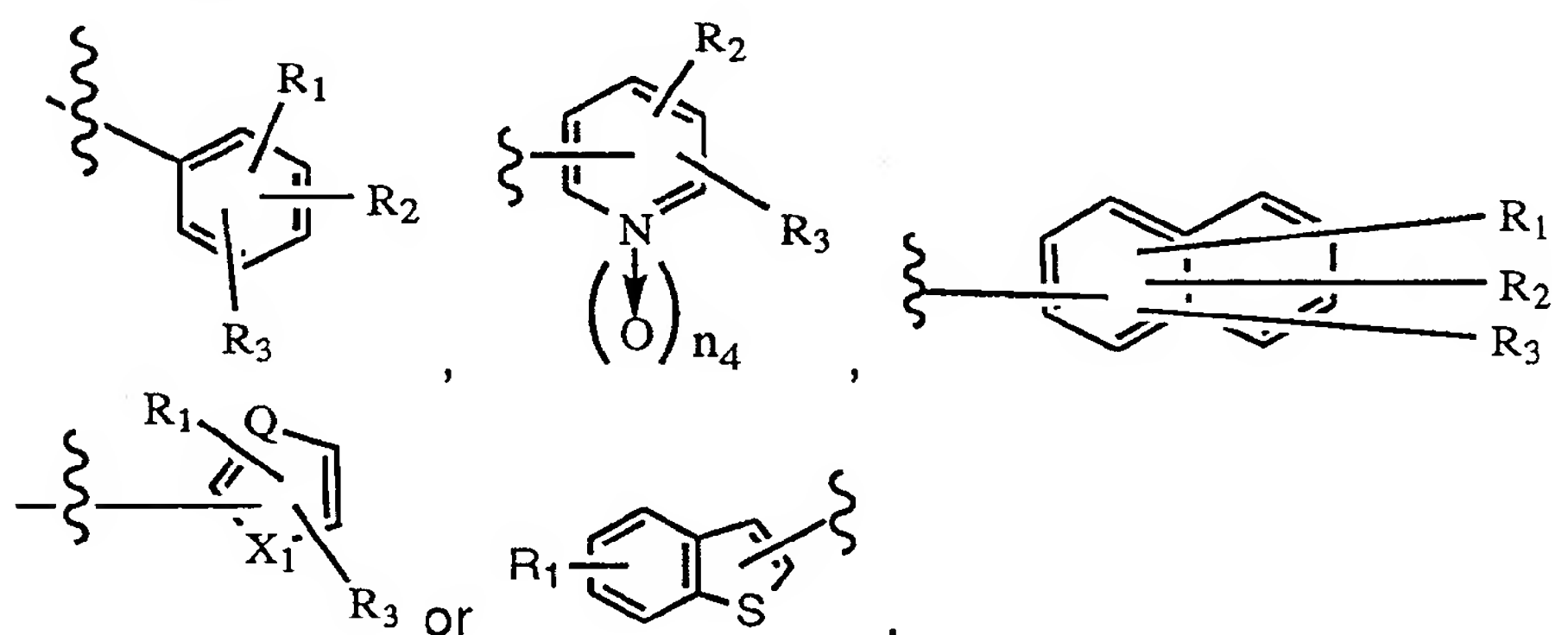
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wherein Q is =N- or =CH-;

- 5 each X_1 is independently -O-, -S- or -NR_a-;
 each X_2 is independently =CH- or -N=; and
 n_4 is 0 or 1; and

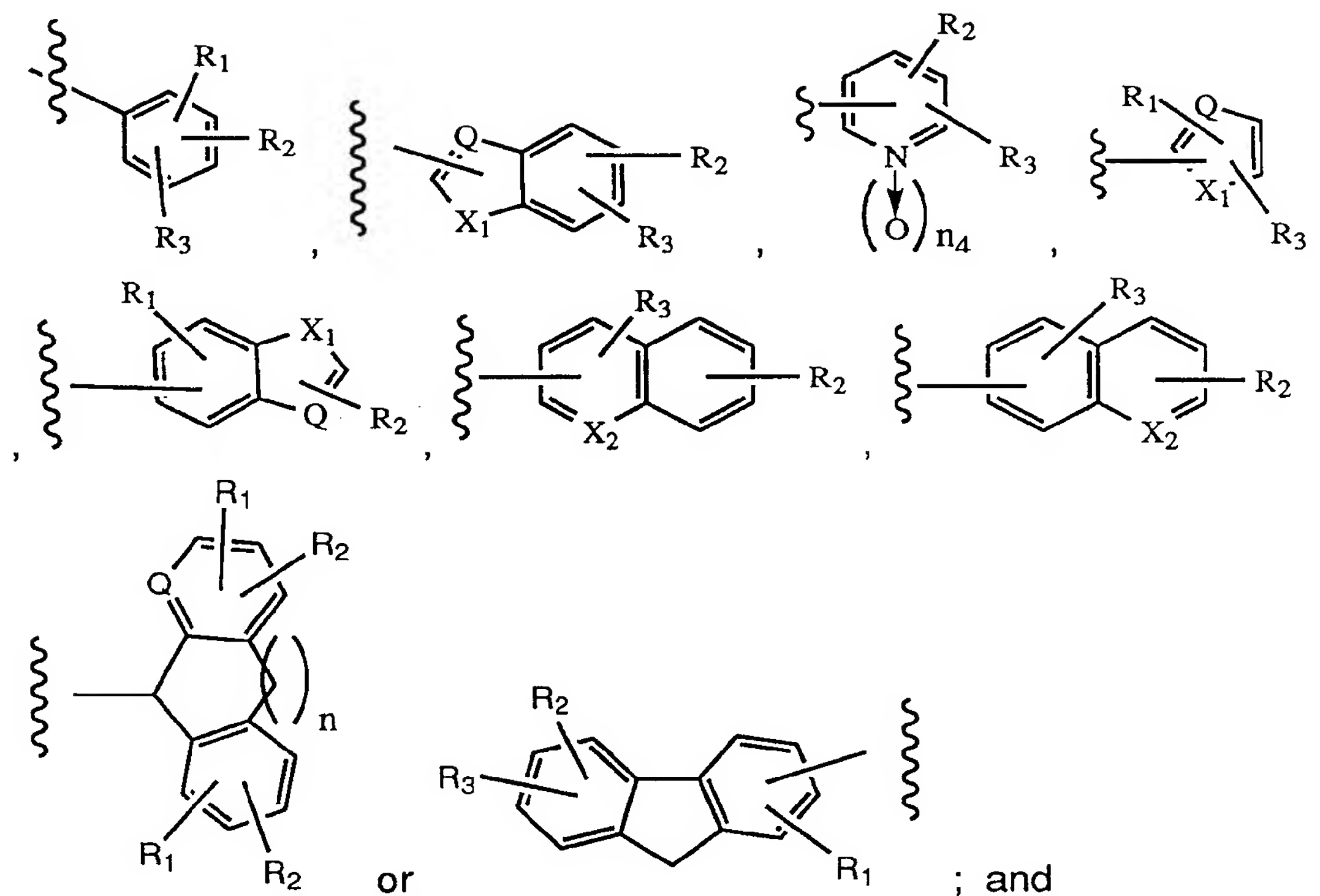
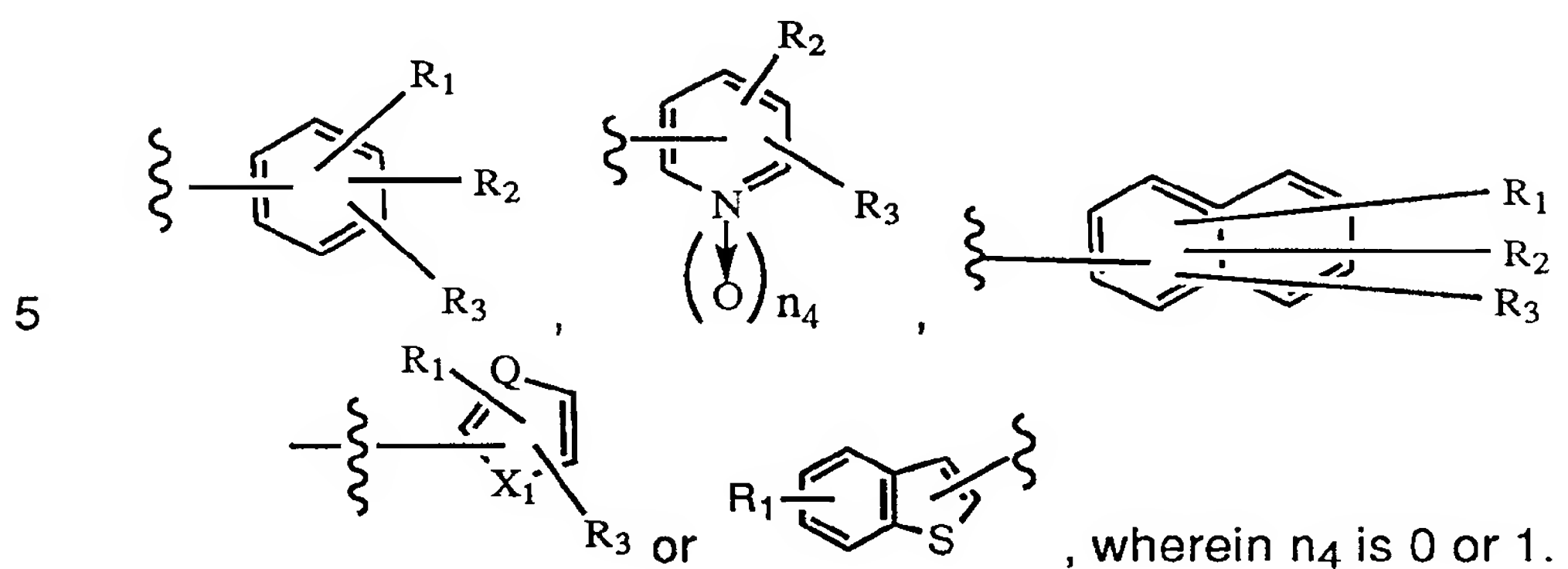
Ar₂ is



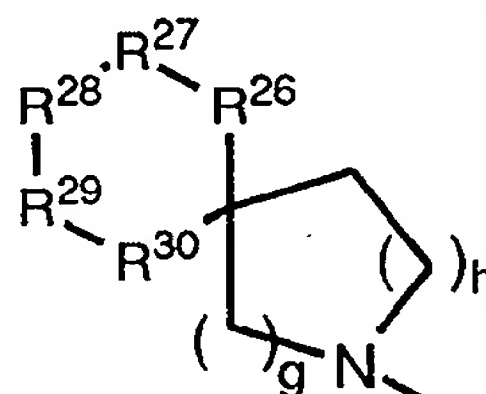
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Also preferred are compounds of formula I wherein each X is =O; l is 0; m is 1; y is 1-3; n is 1; u is 0; Ar₁ is

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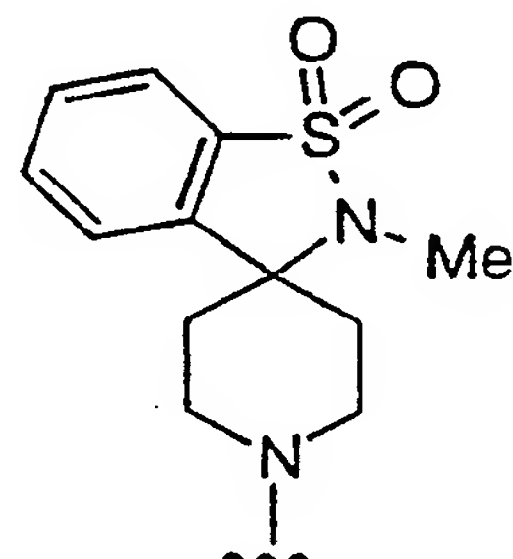
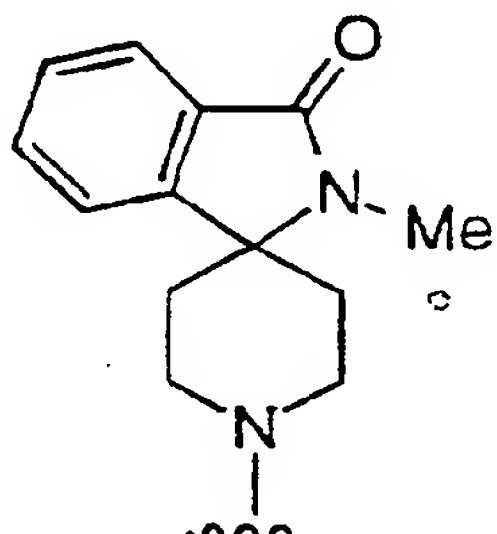
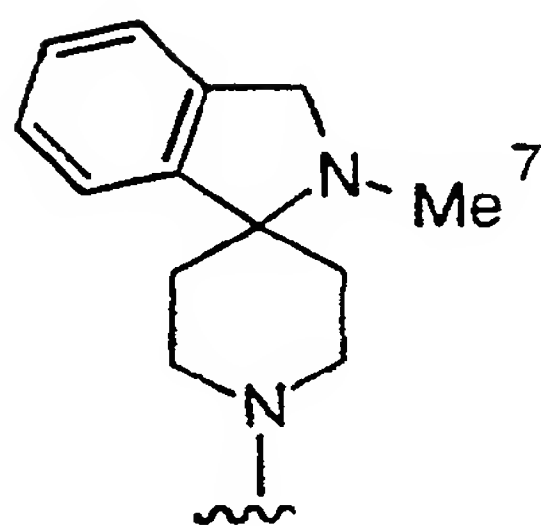
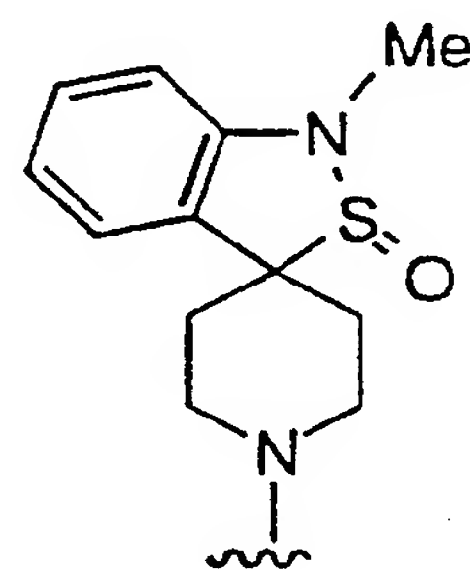
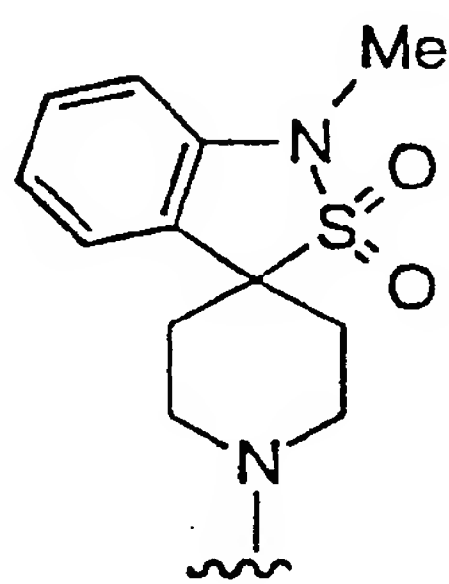
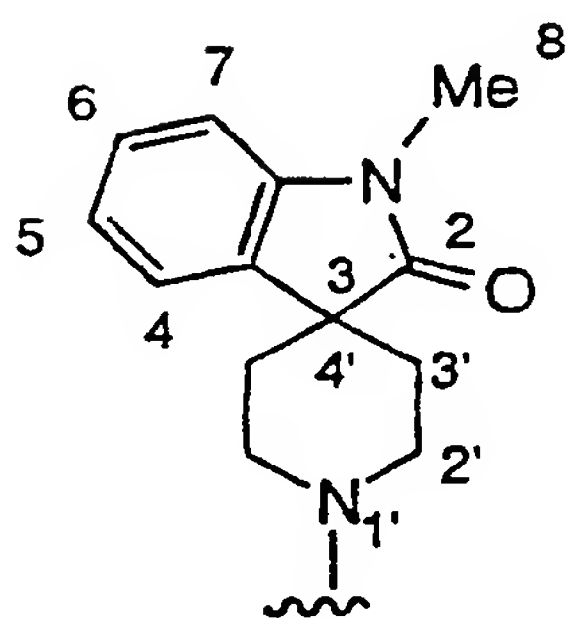
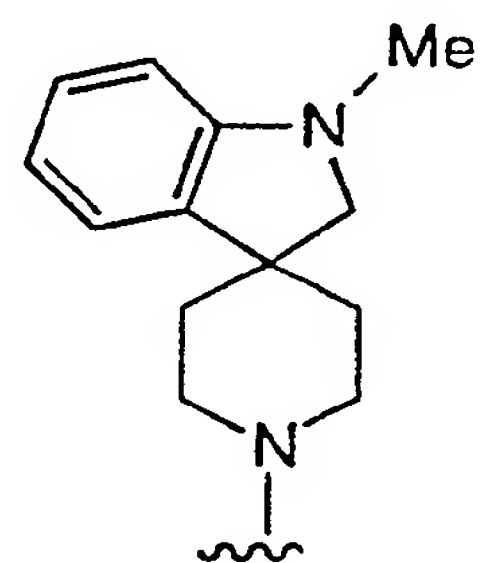
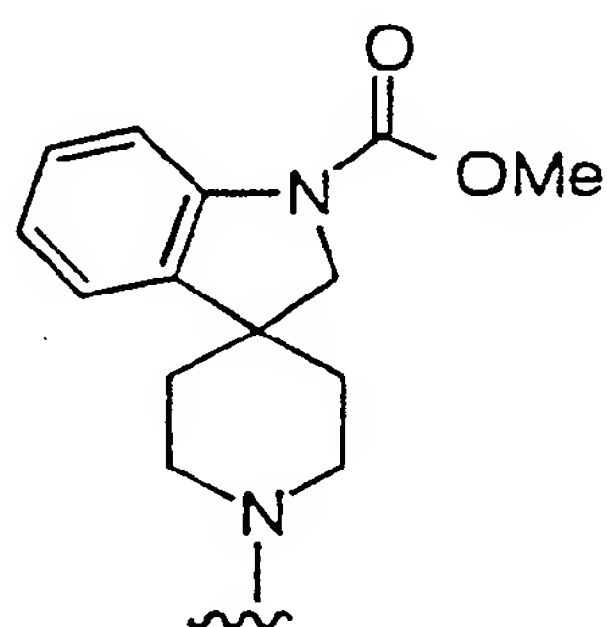
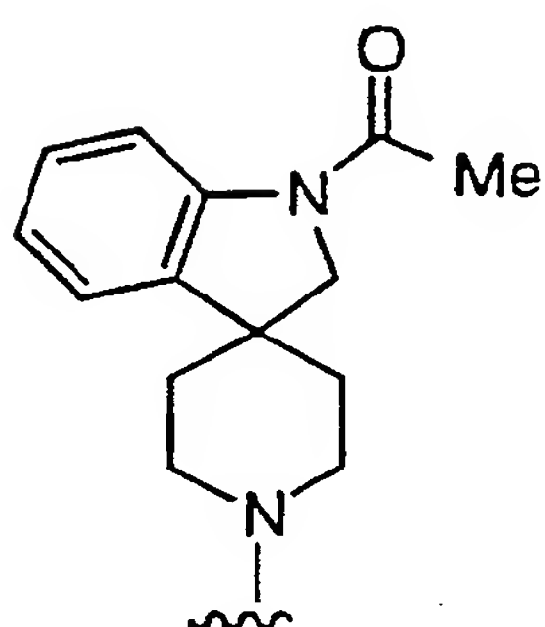
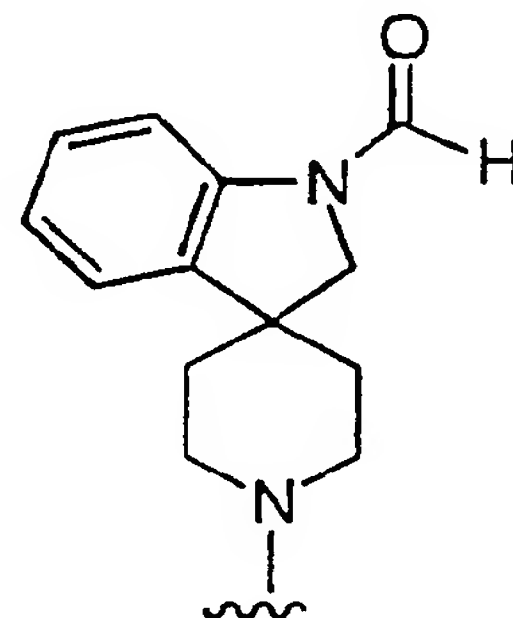
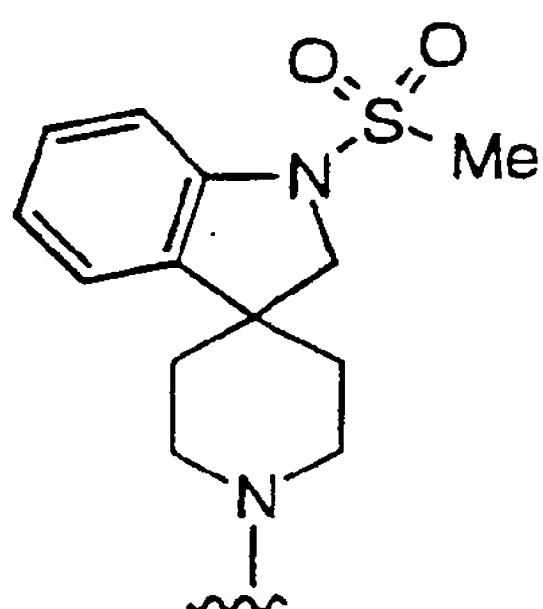
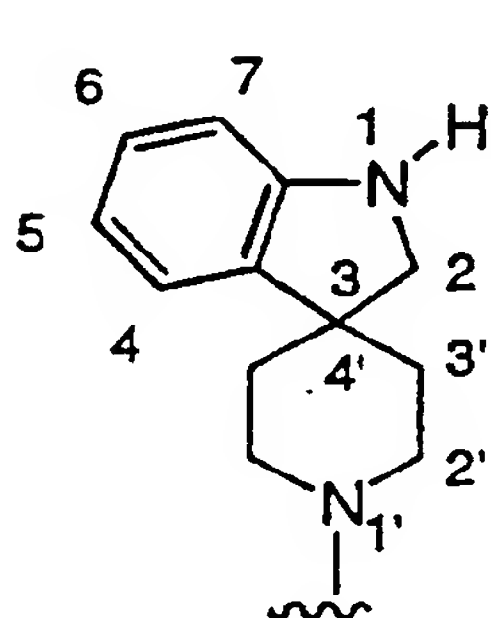
 Ar_2 is

Preferred definitions of Z having the spirocyclic structure

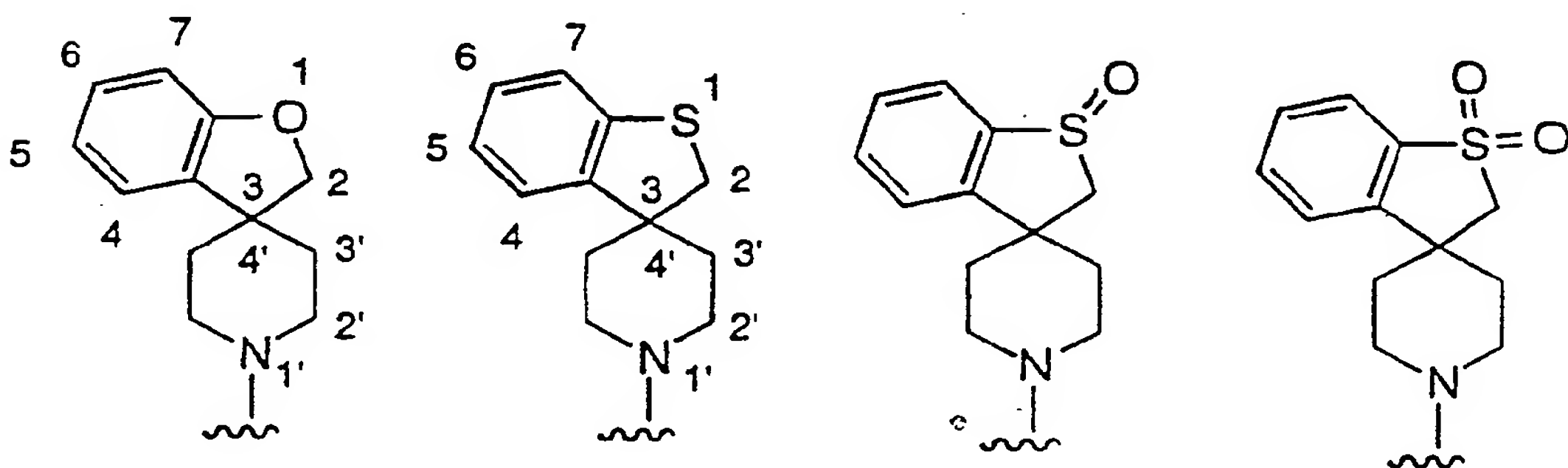
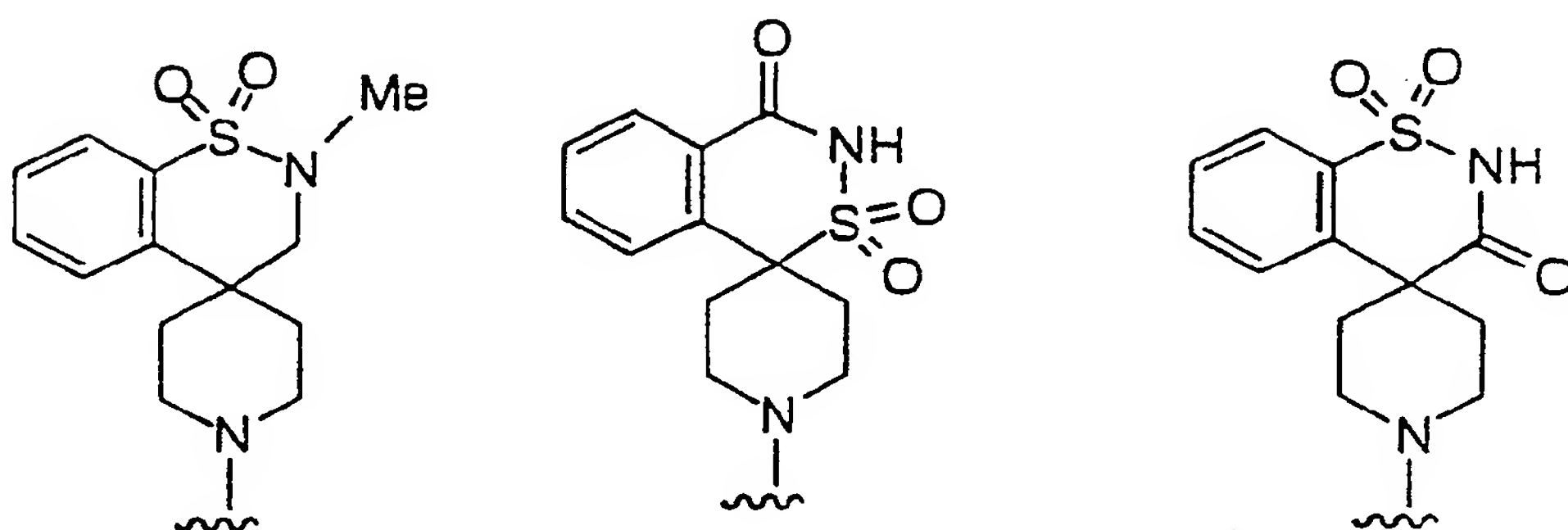
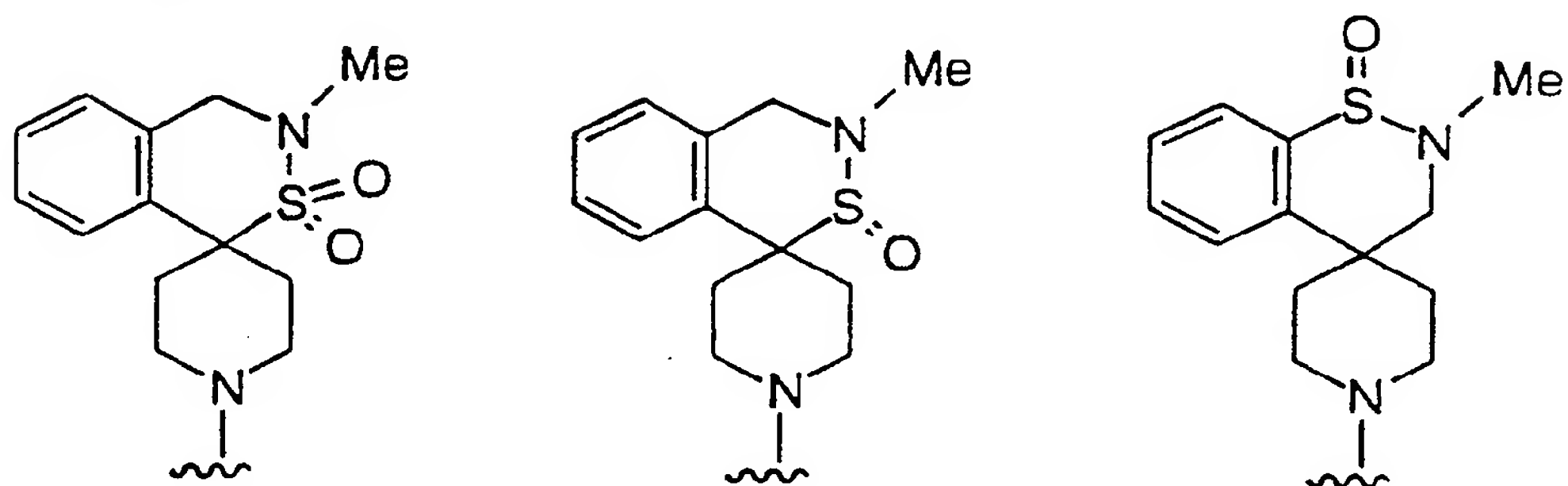
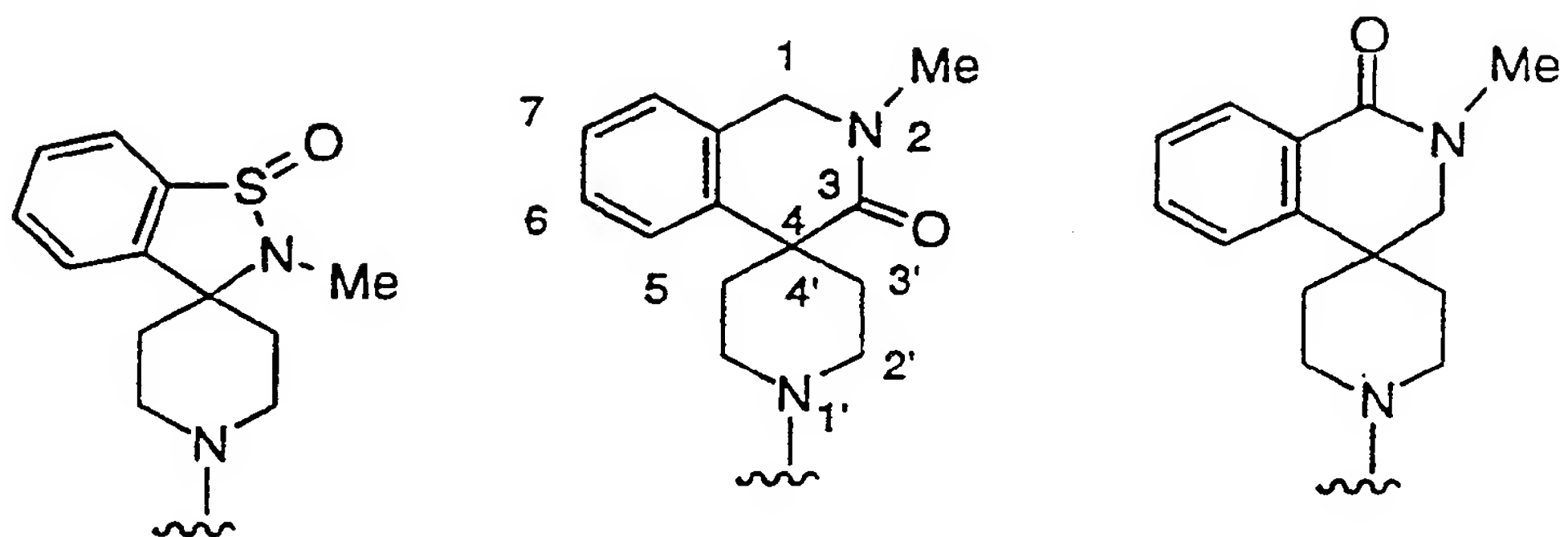


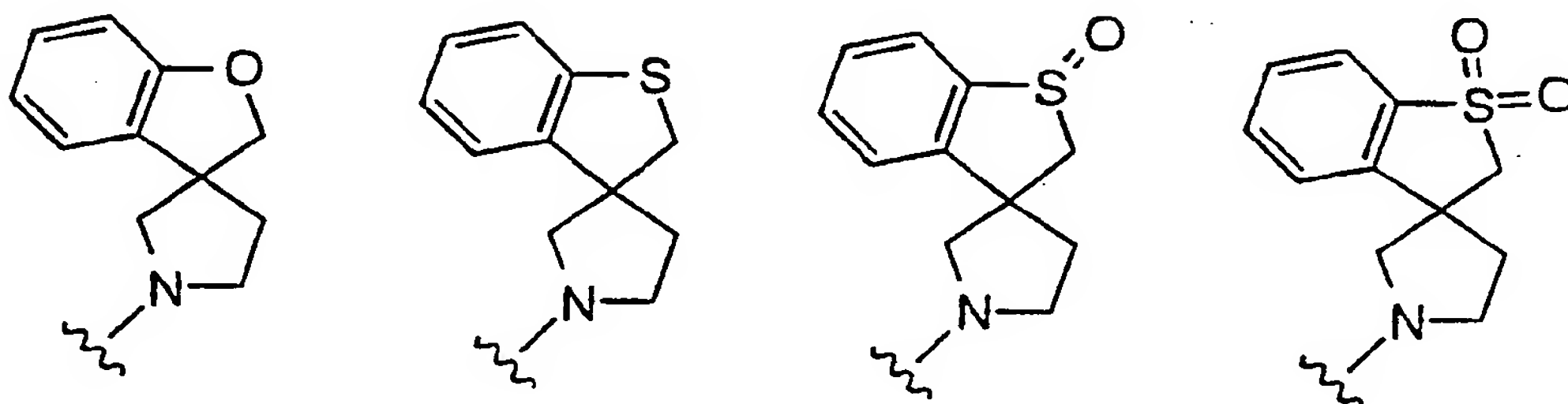
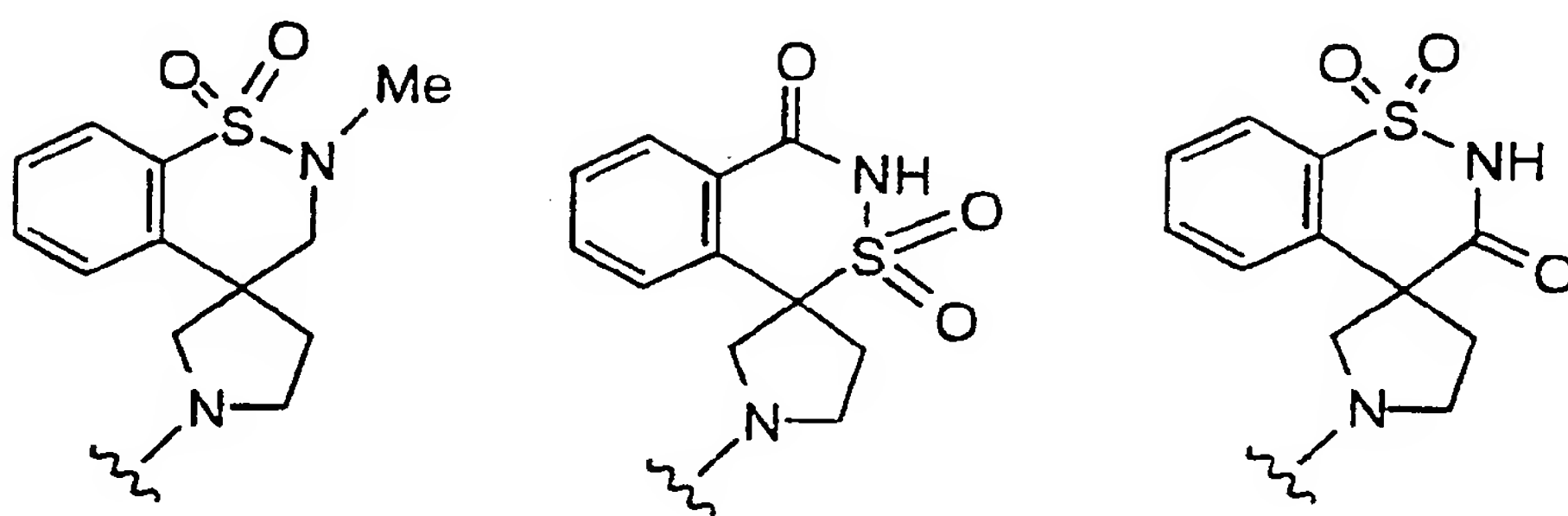
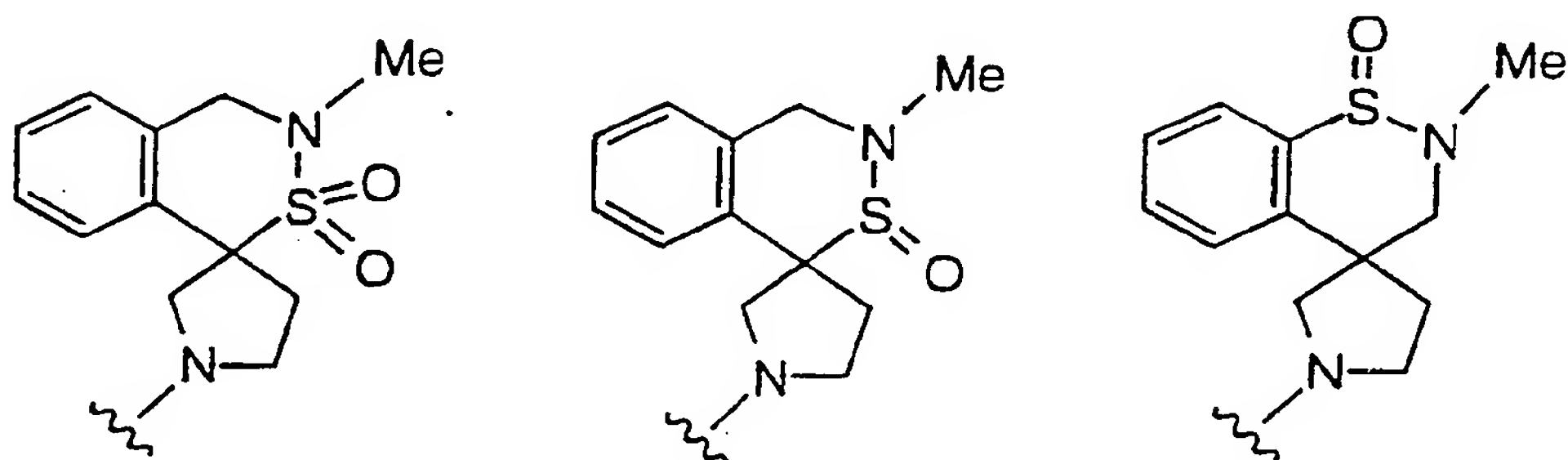
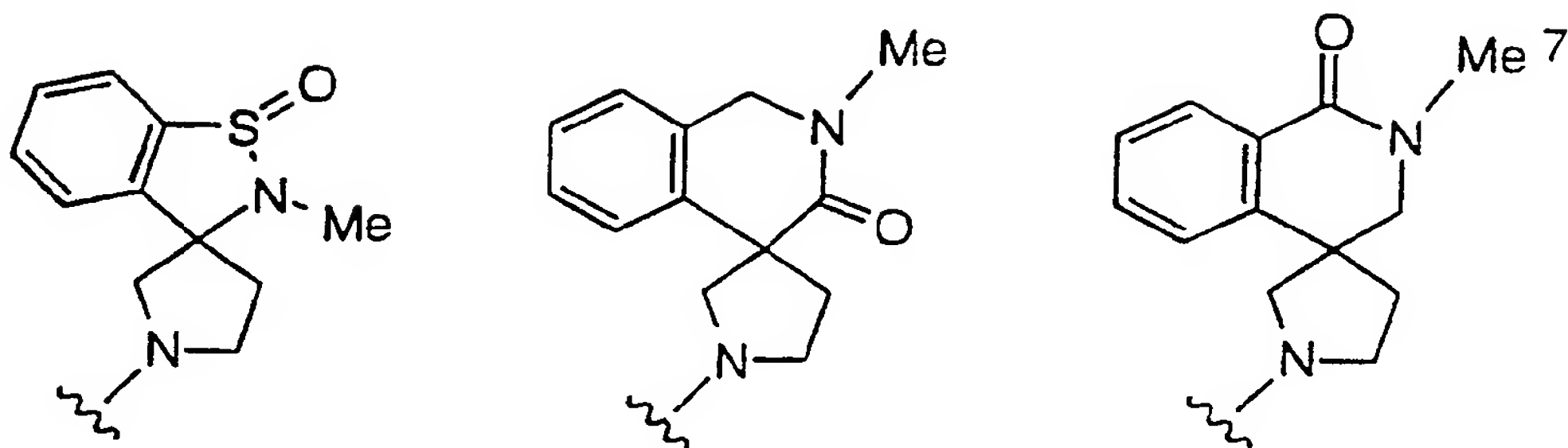
are exemplified by the following structures, optionally substituted at the
 10 positions indicated by numbers 1-8 with $-OH$, $=O$, $-CN$, $-NR^{35}R^{36}$,
 $-NHCOR^{35}R^{36}$, halogeno, $-CF_3$, phenyl, mono, di or trisubstituted

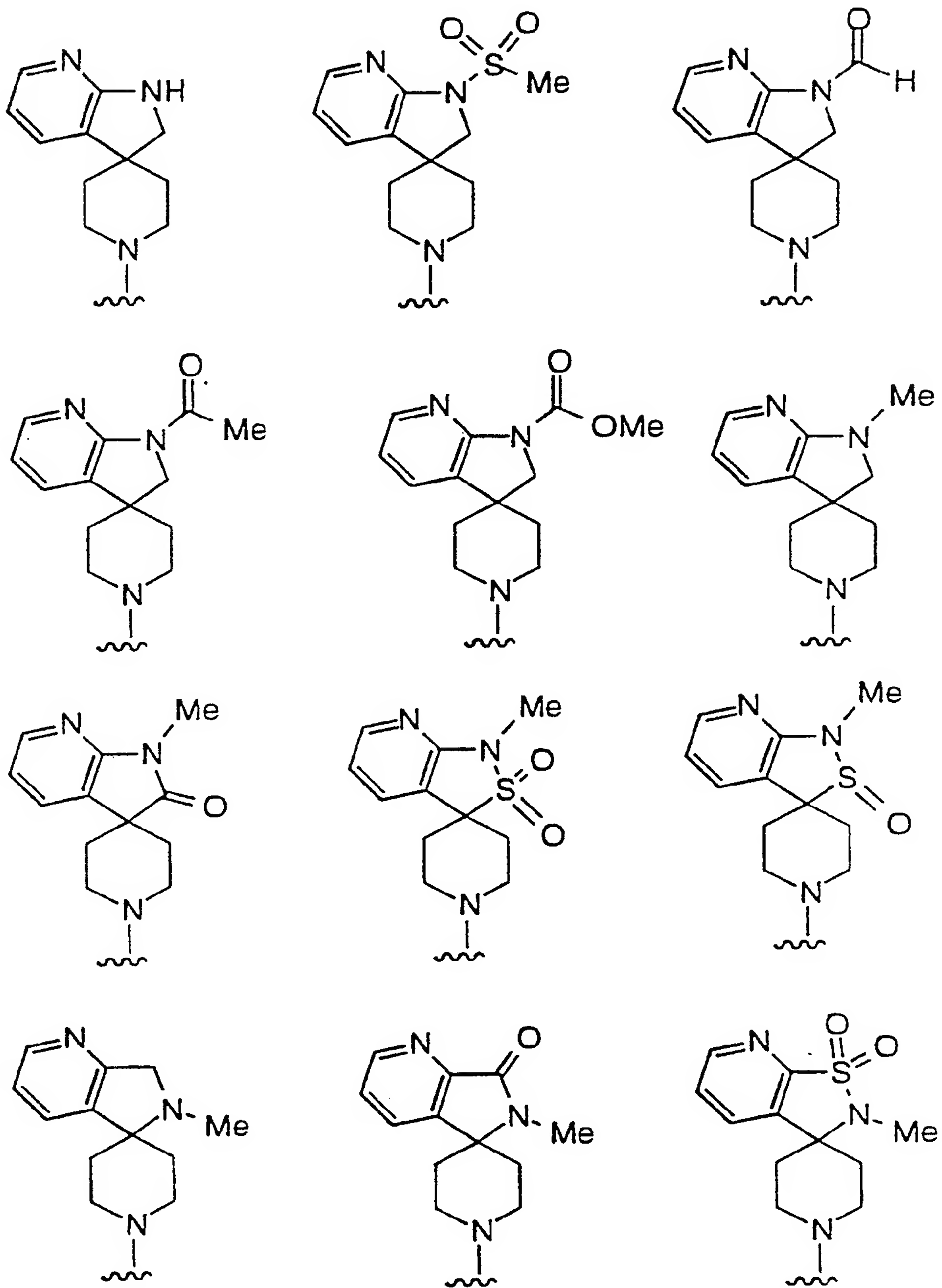
phenyl, wherein the phenyl substituents are independently selected from the group of substituents defined immediately above and C₁₋₃ alkyl:



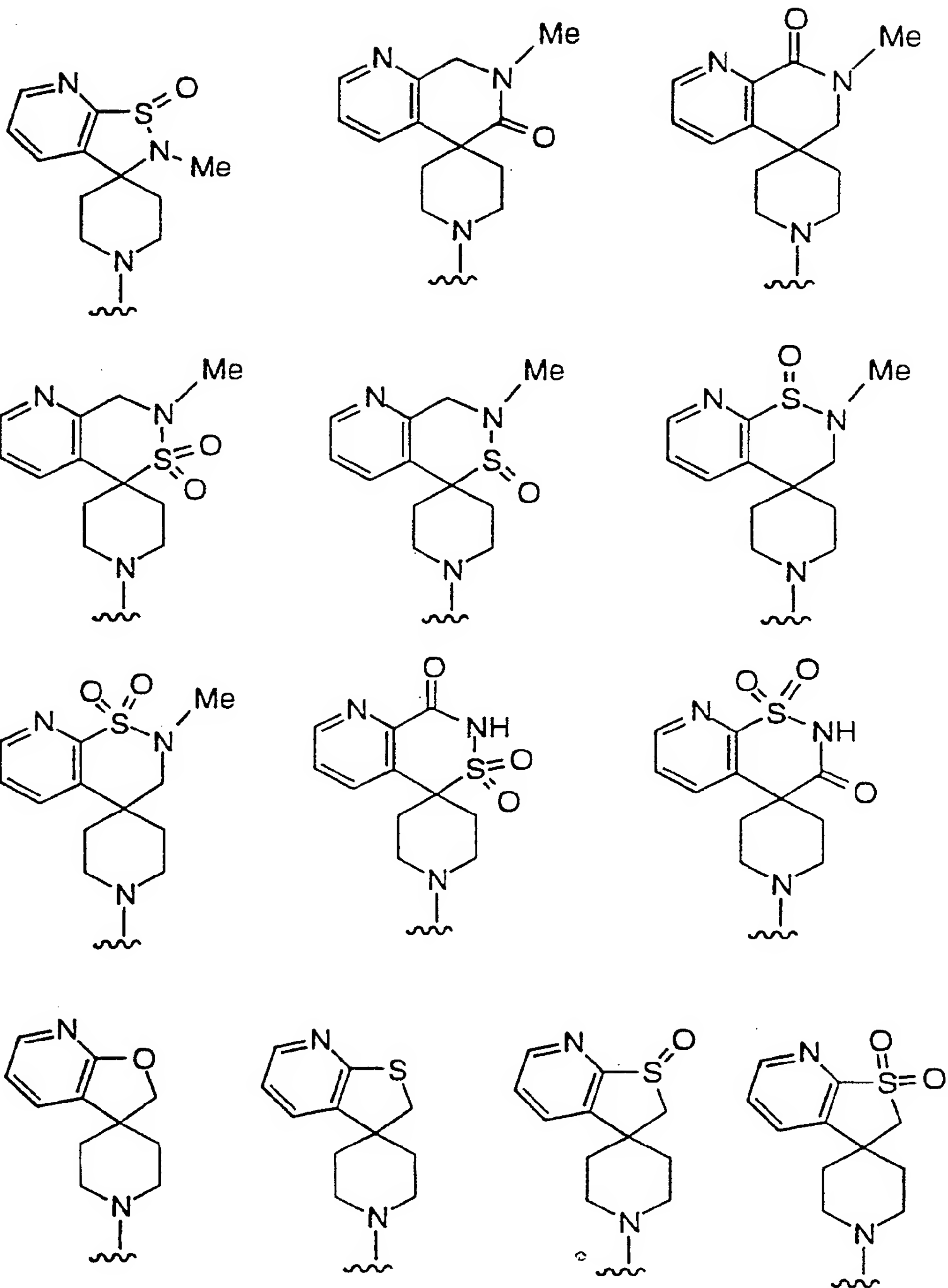
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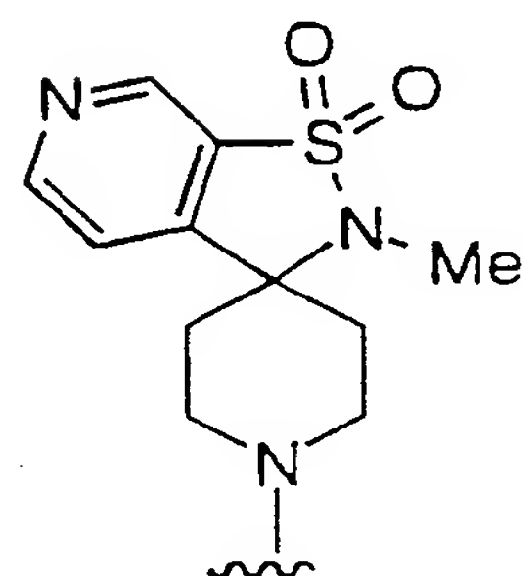
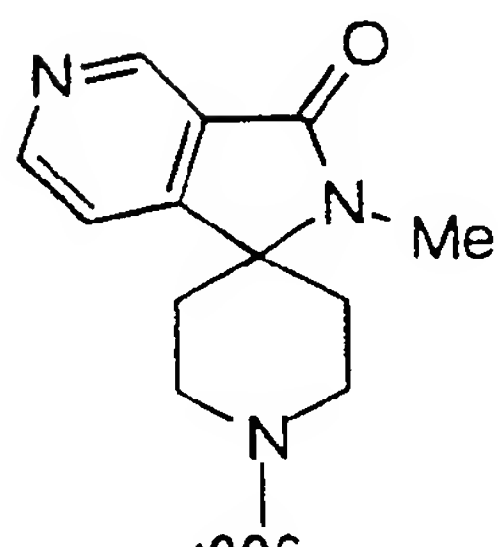
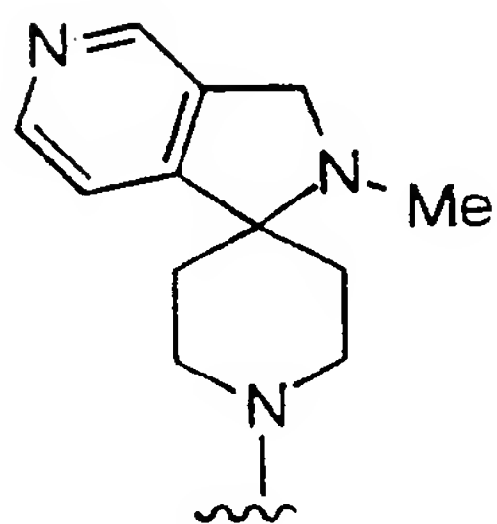
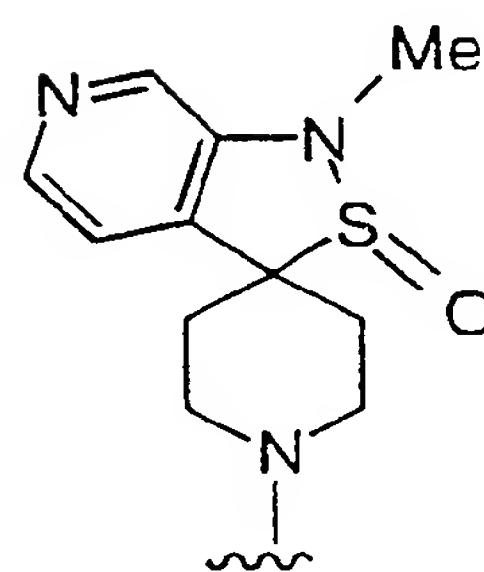
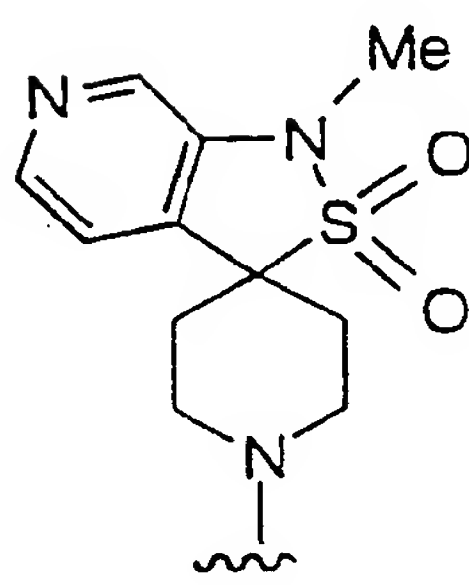
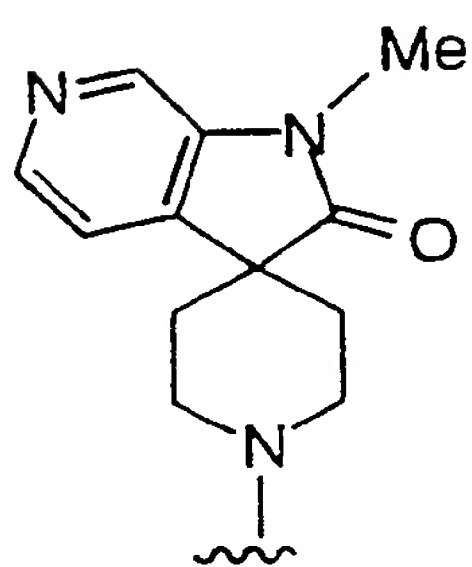
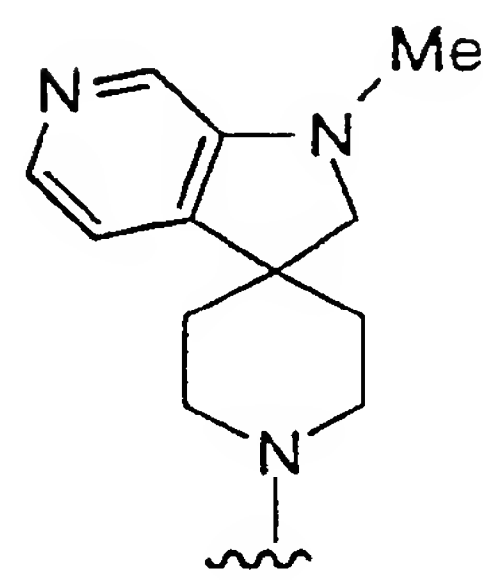
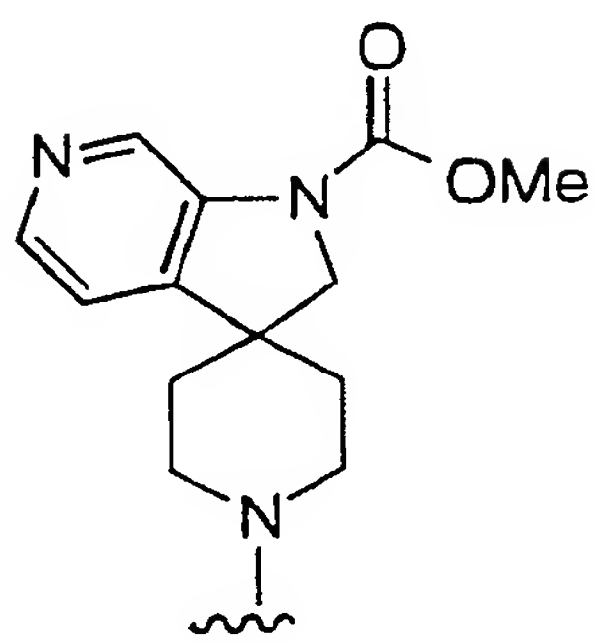
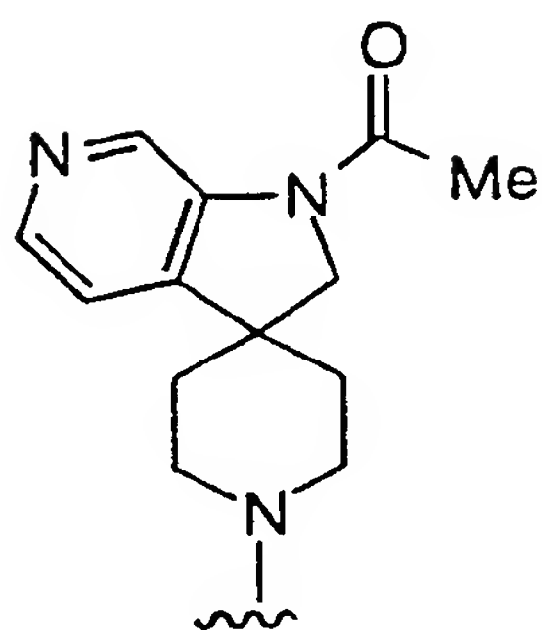
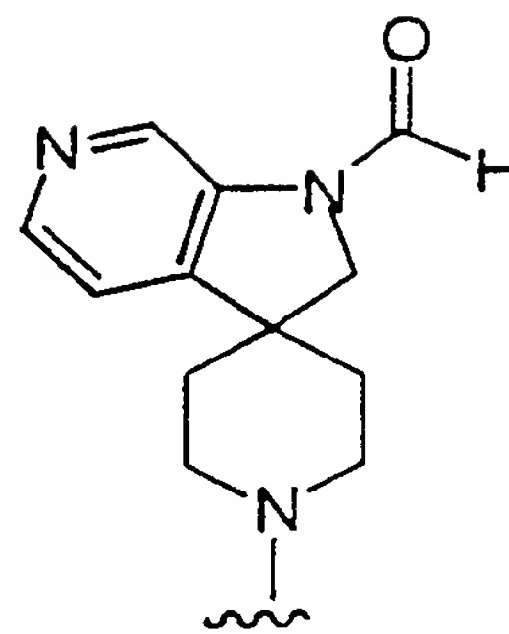
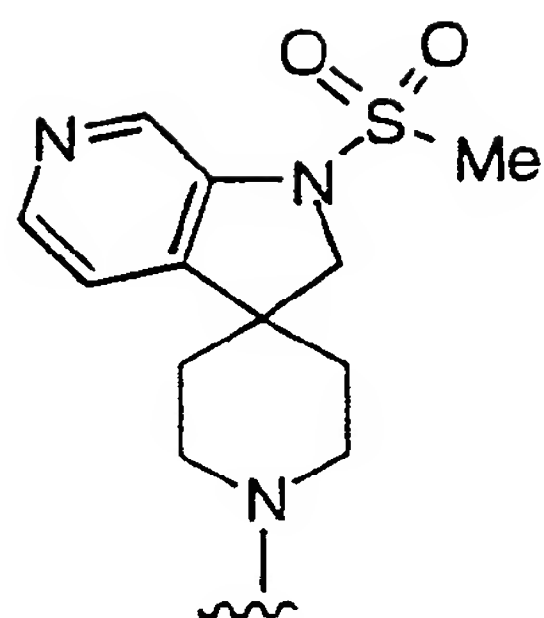
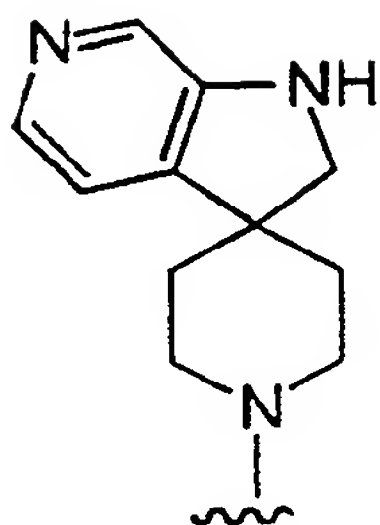


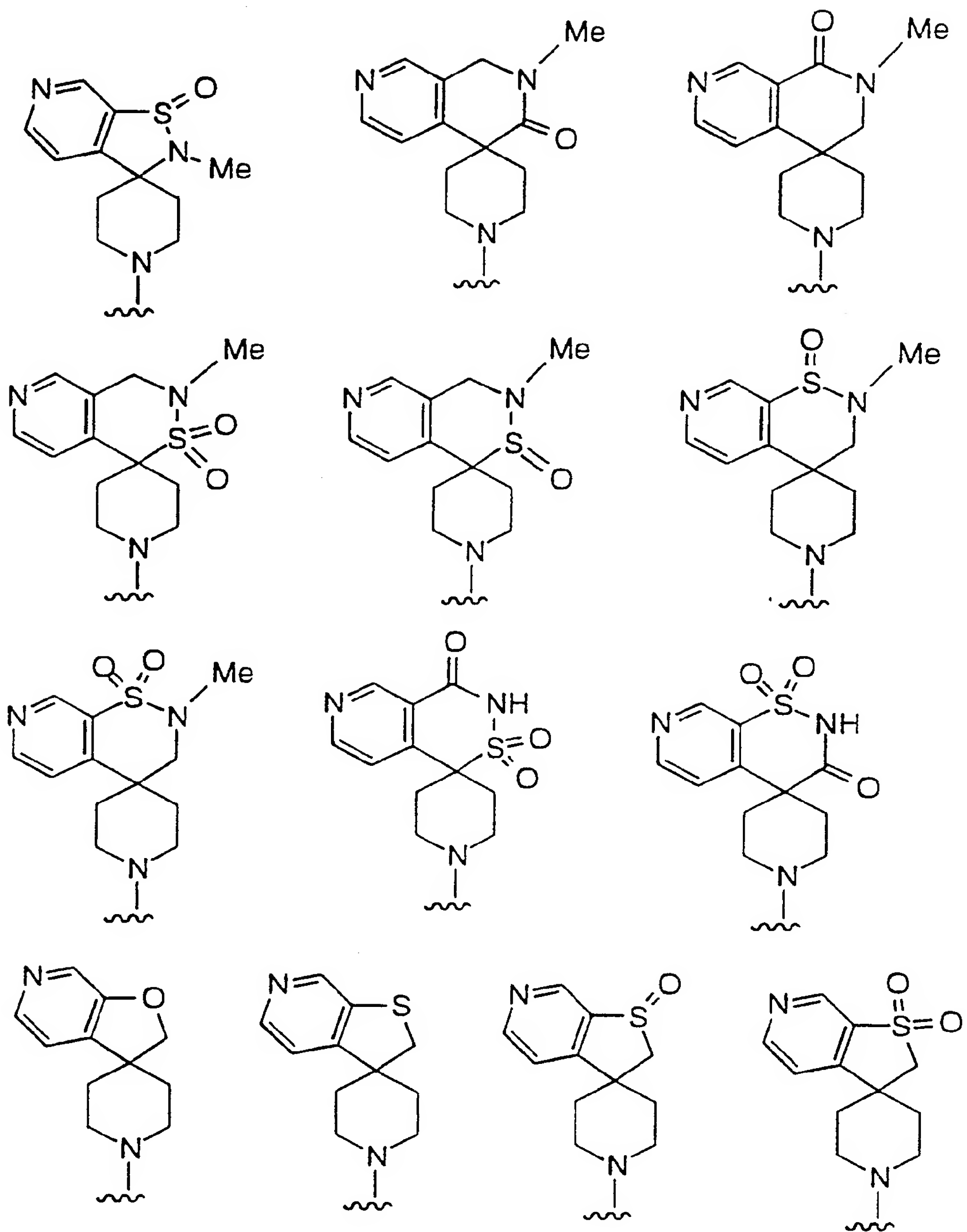


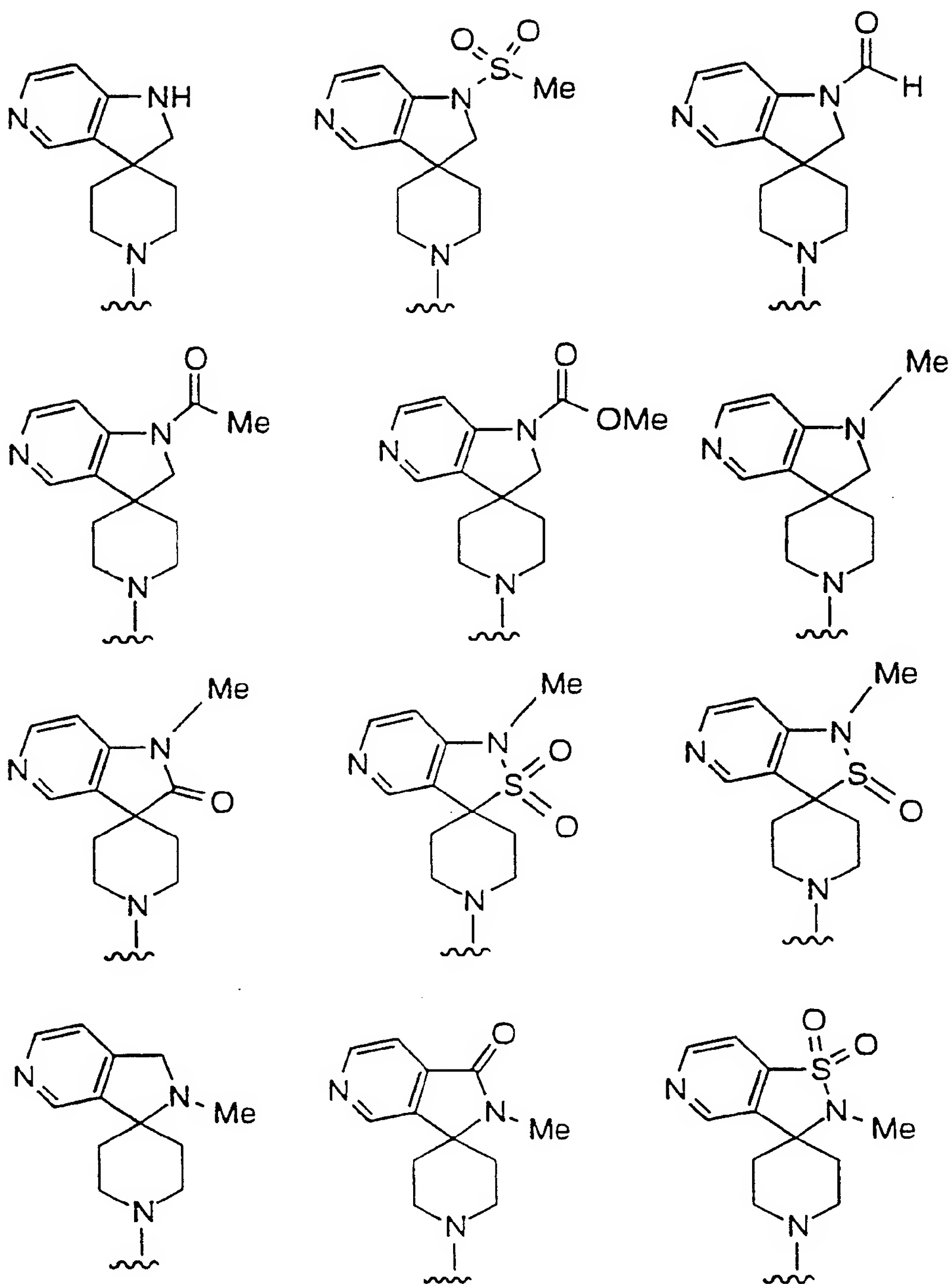


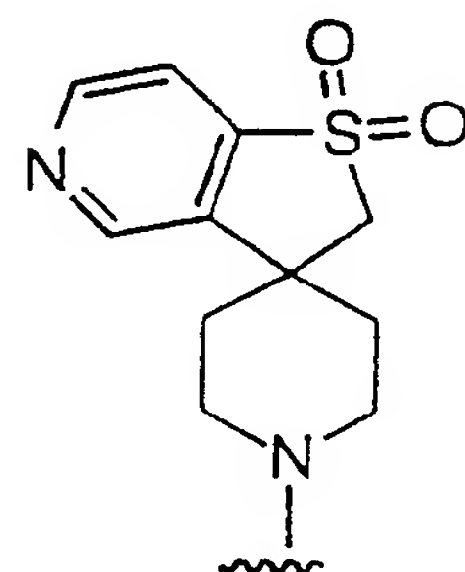
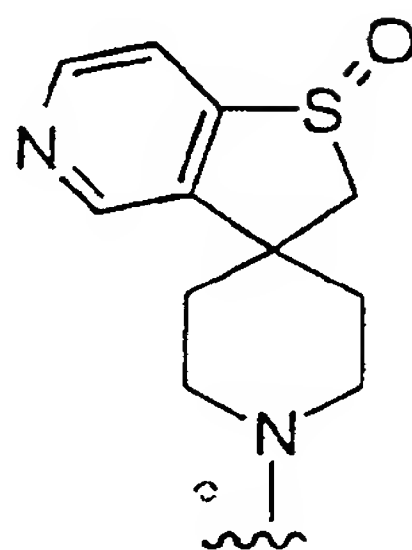
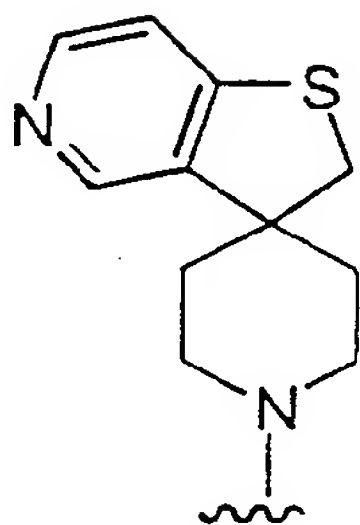
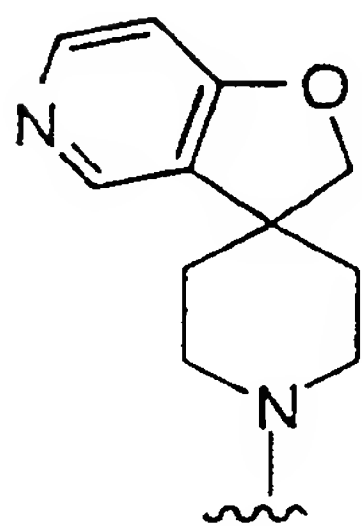
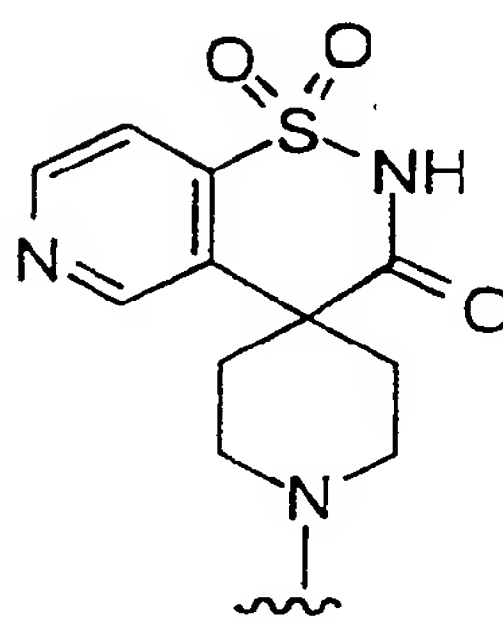
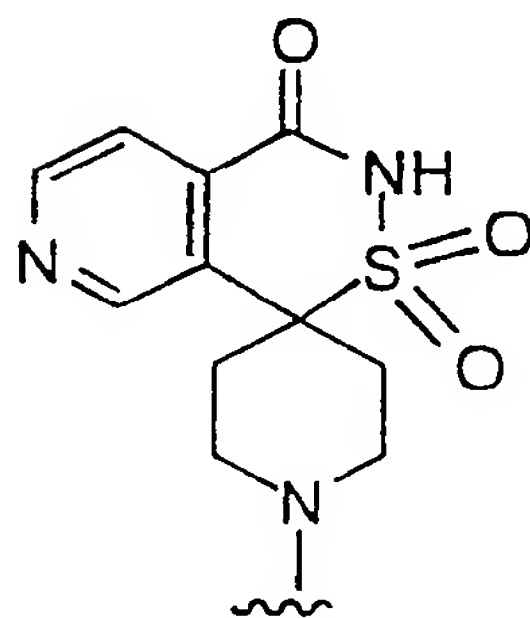
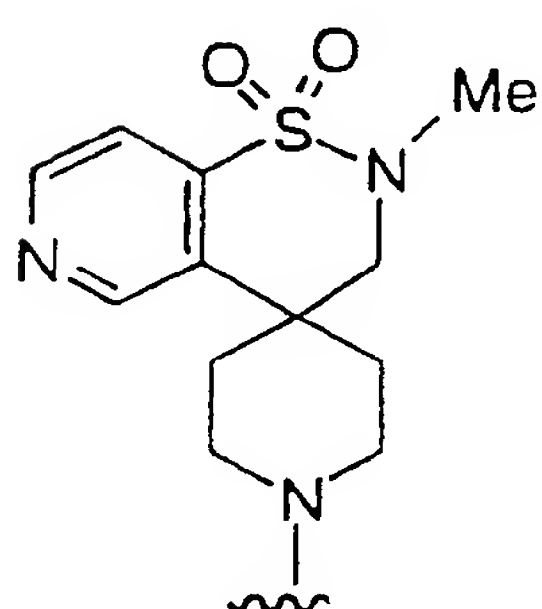
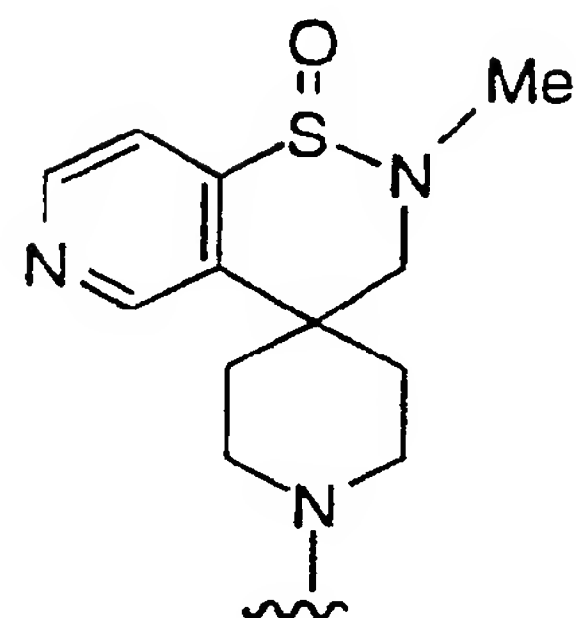
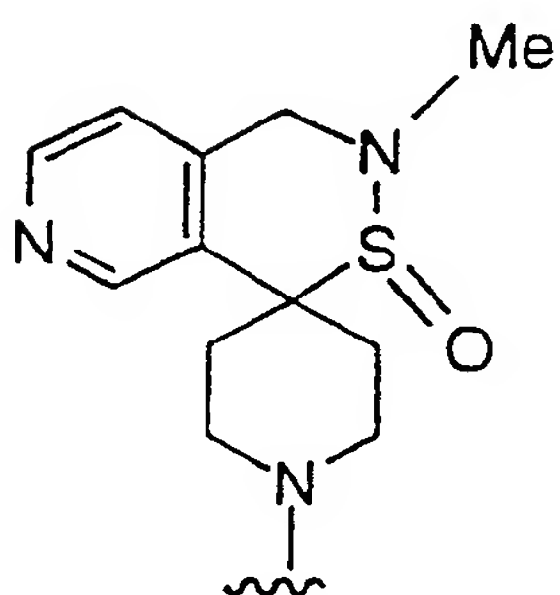
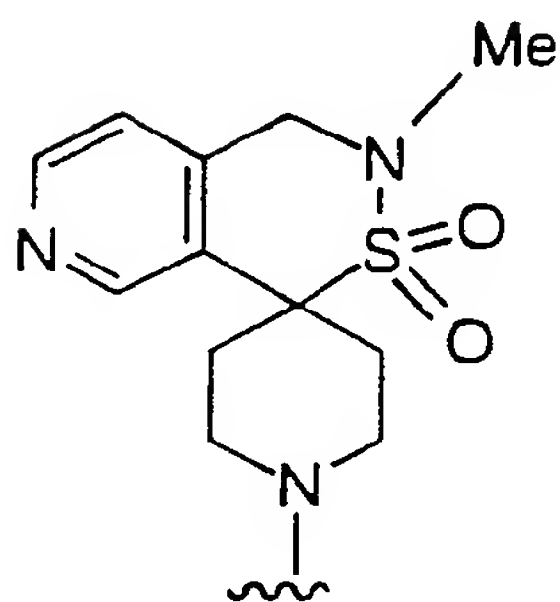
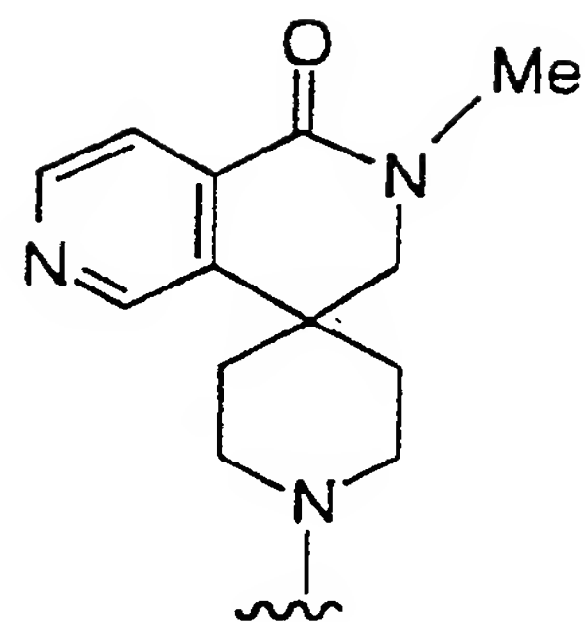
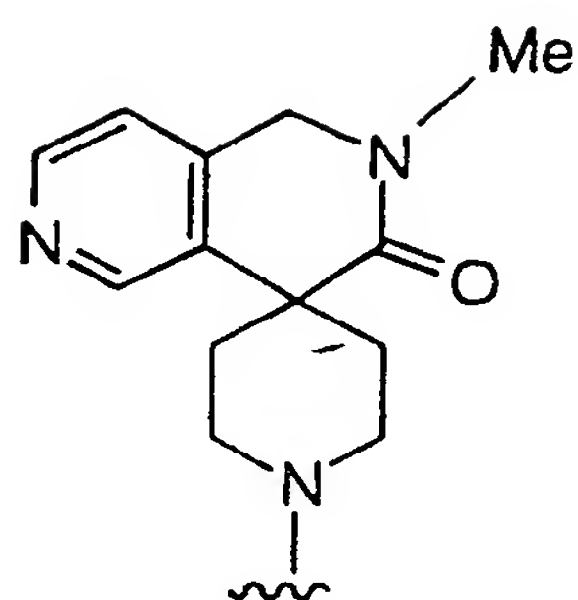
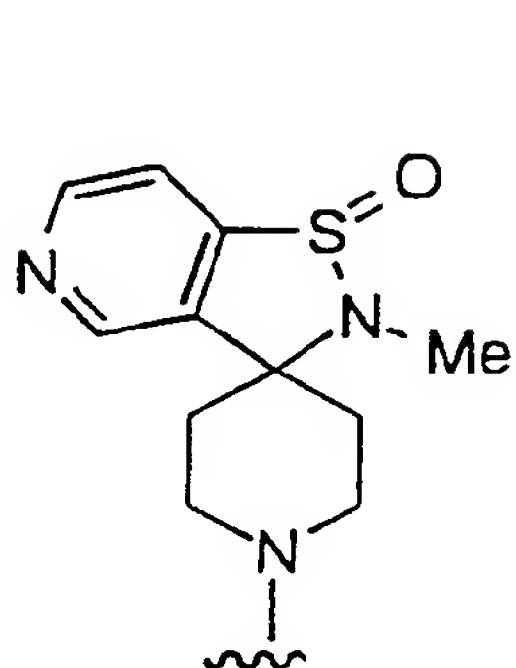
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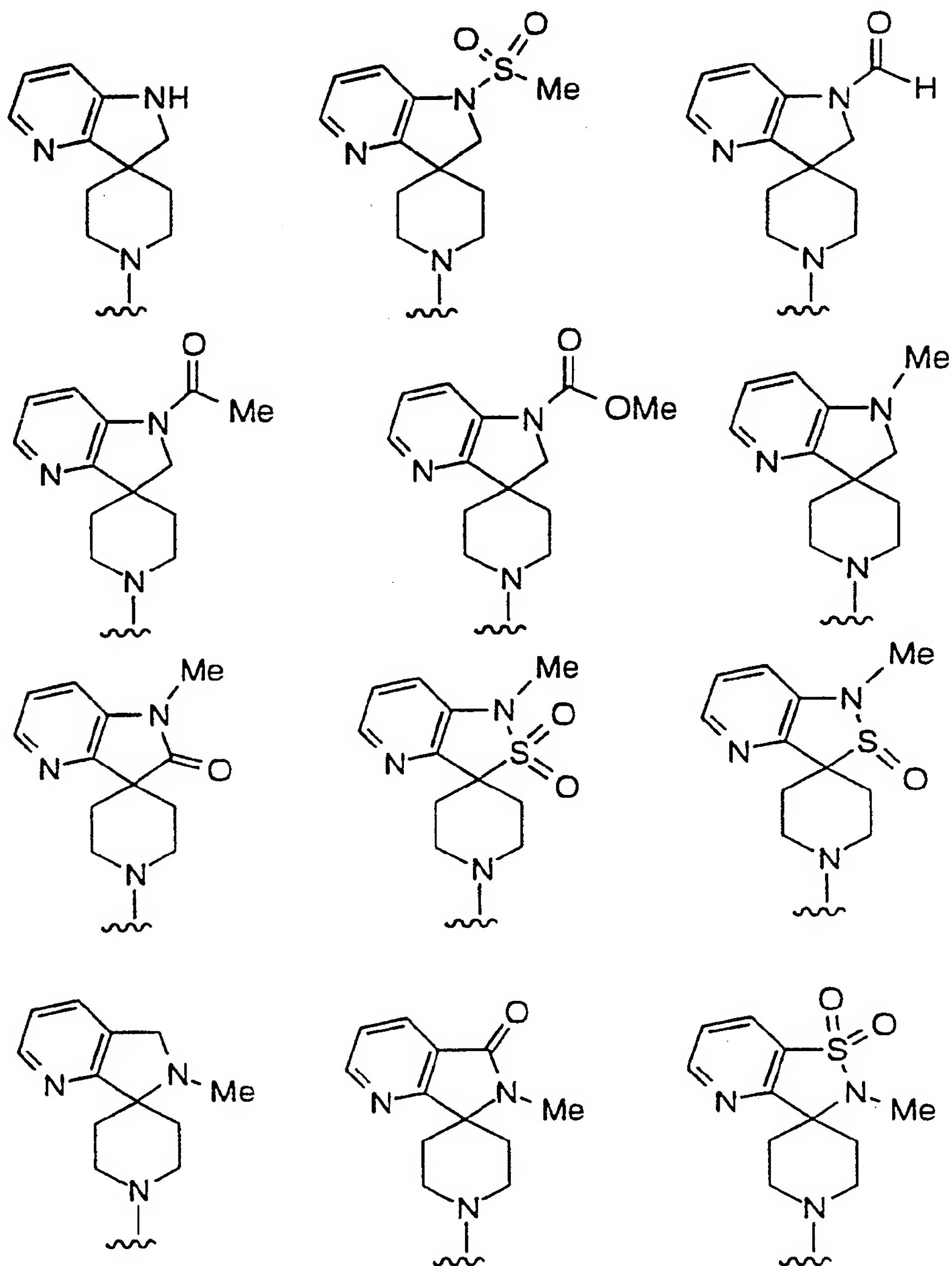


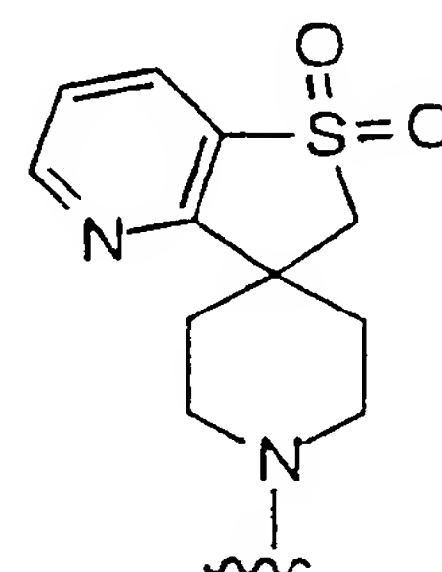
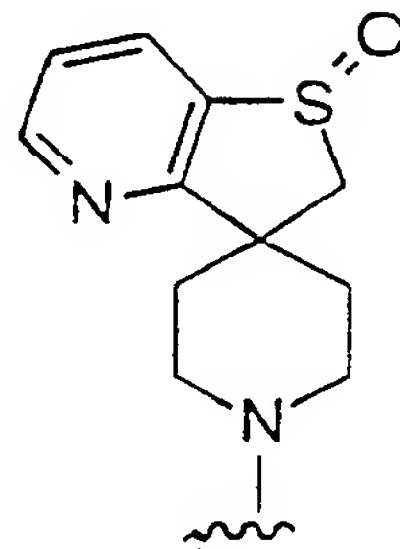
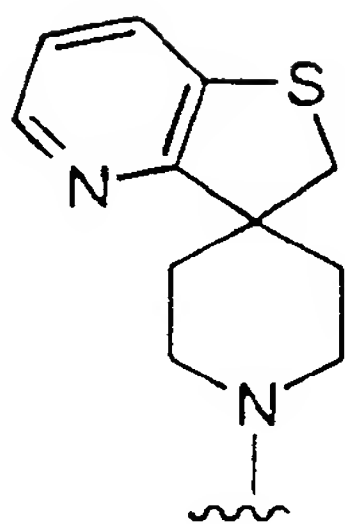
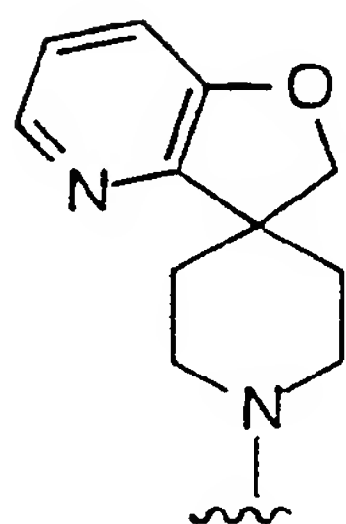
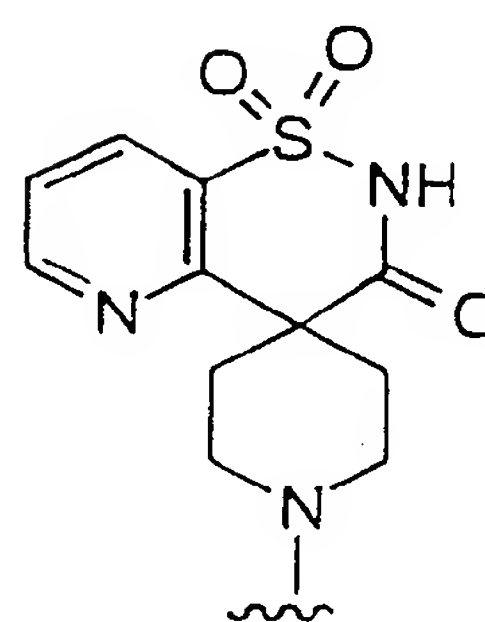
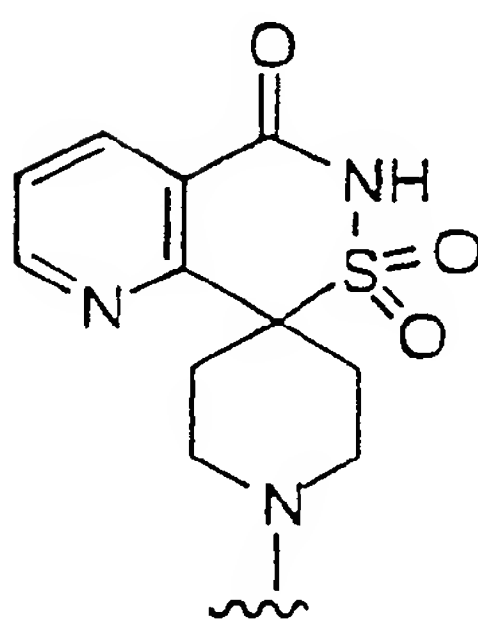
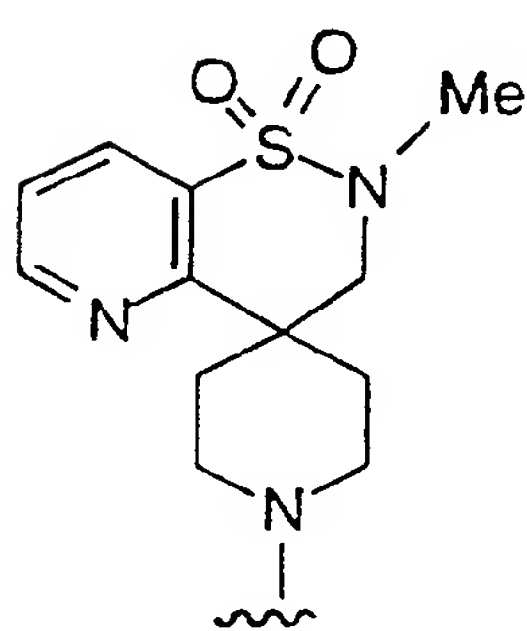
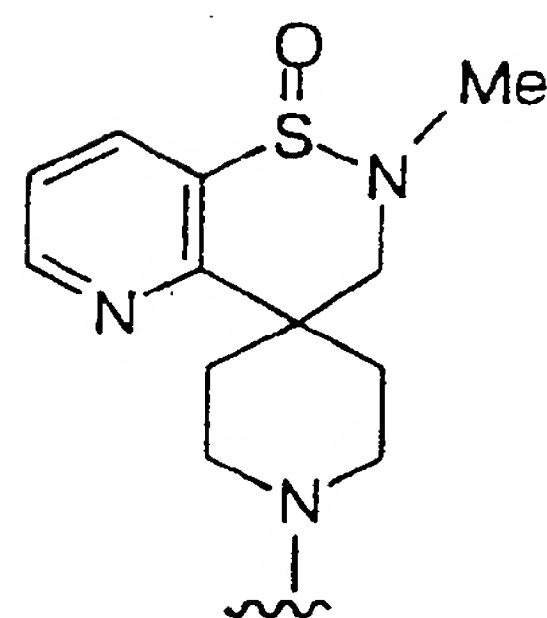
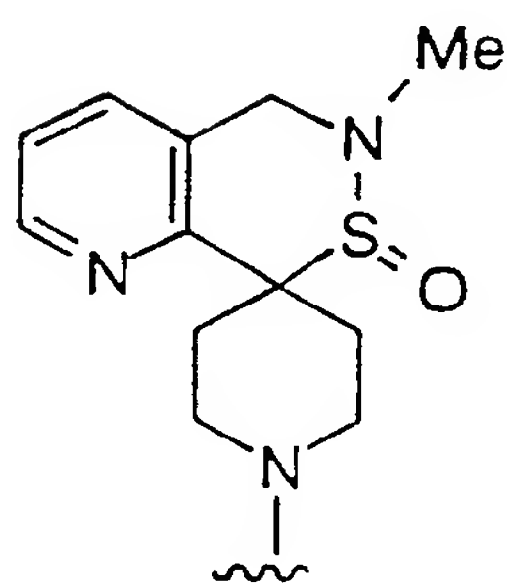
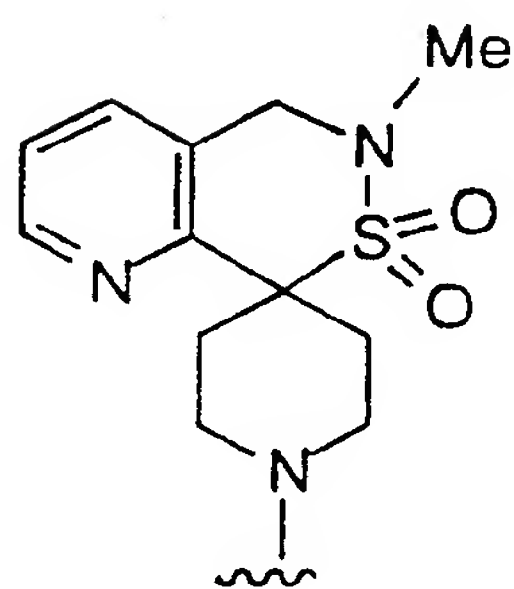
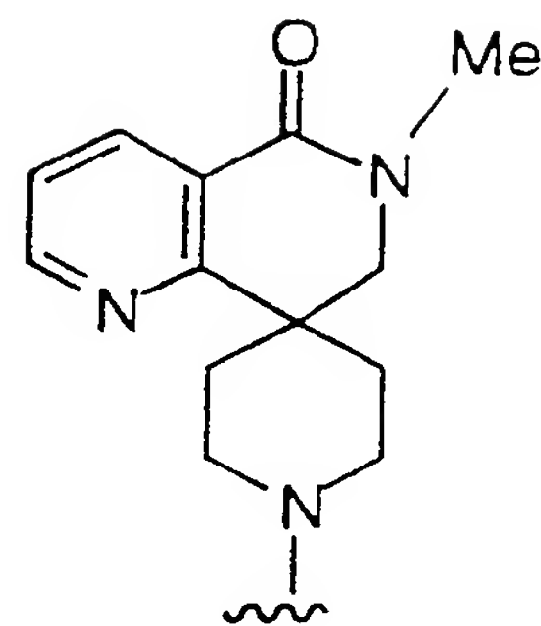
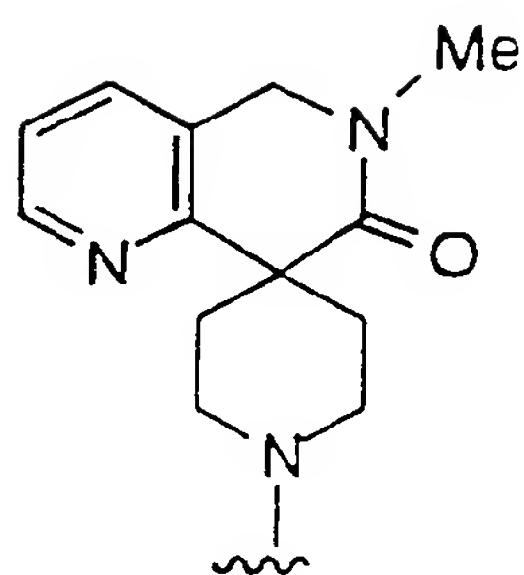
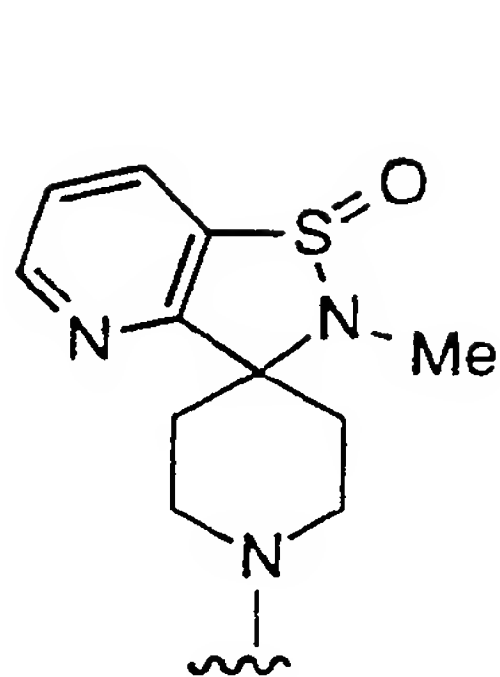


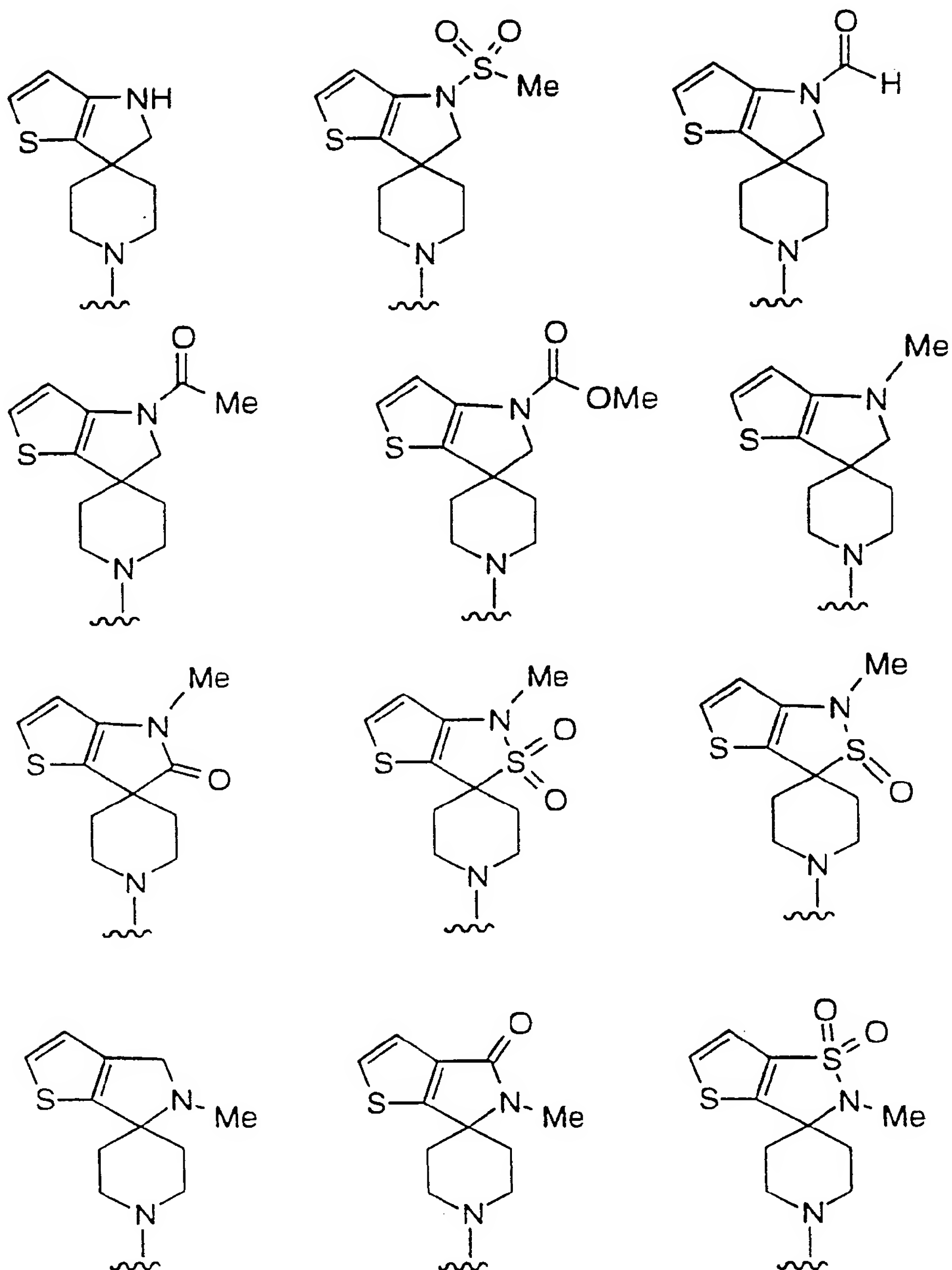


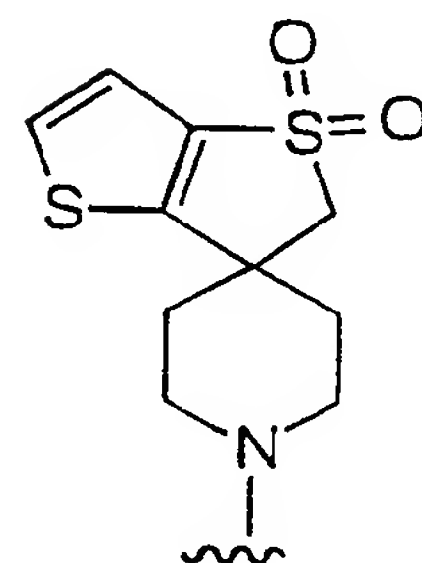
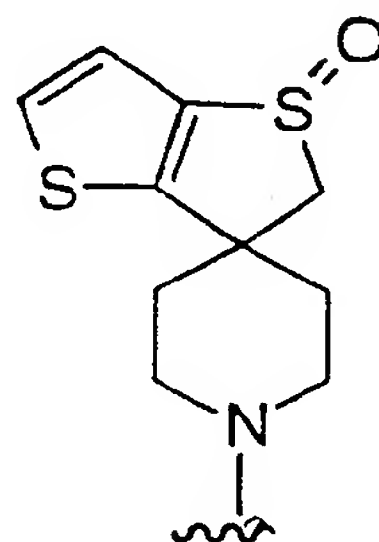
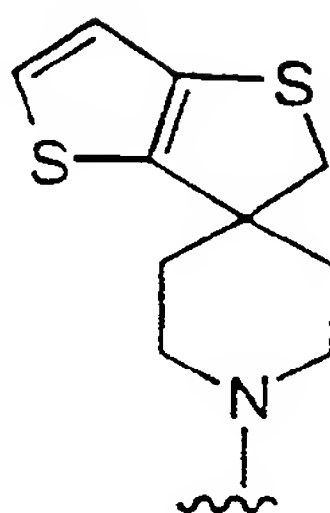
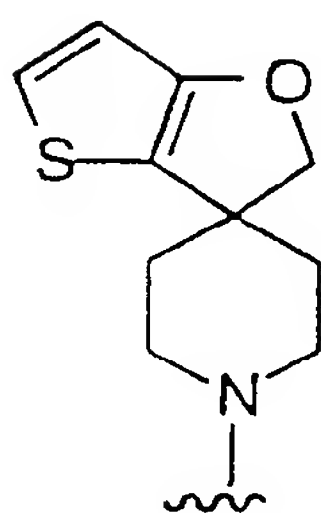
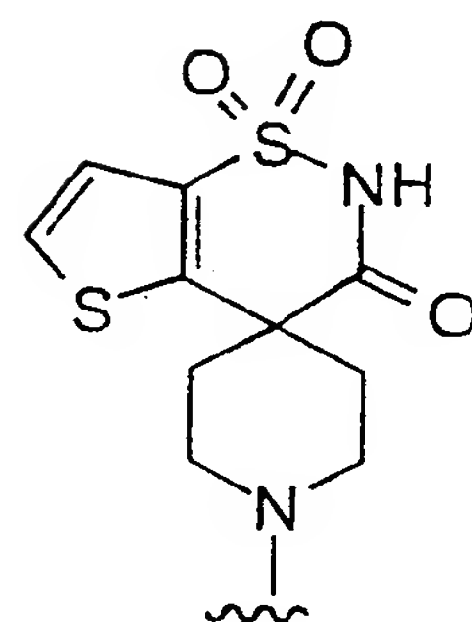
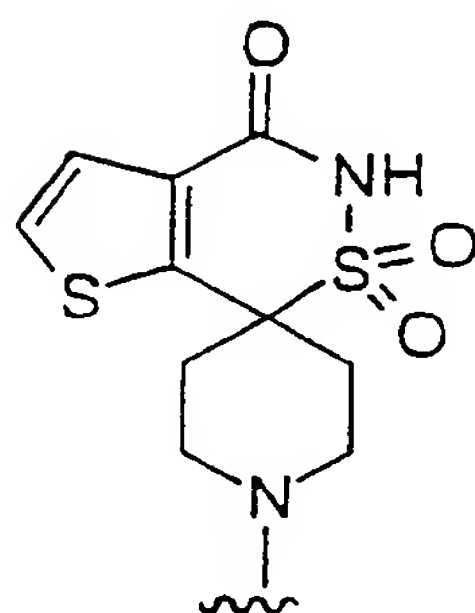
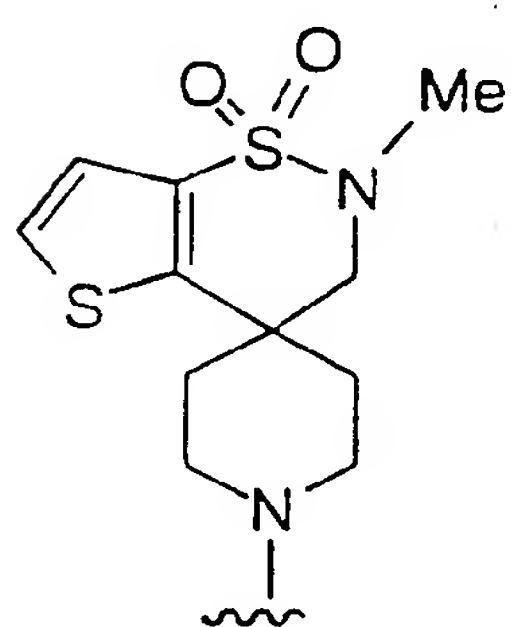
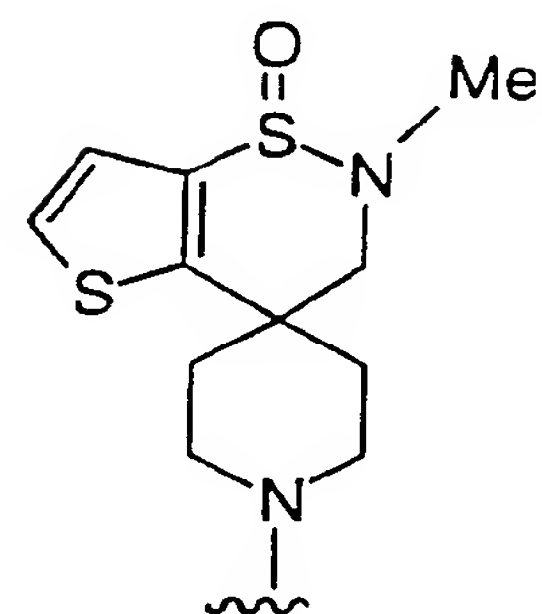
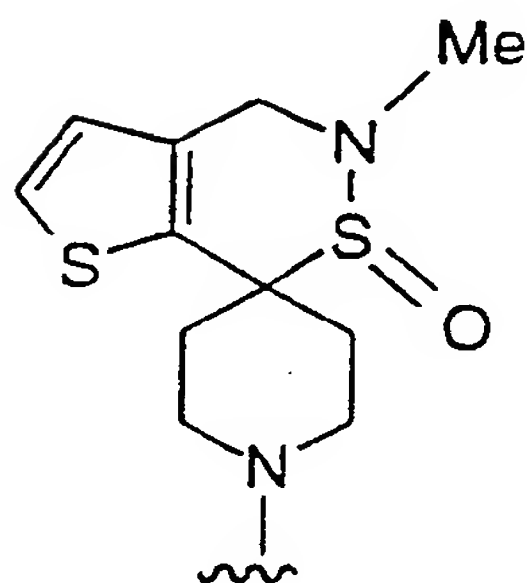
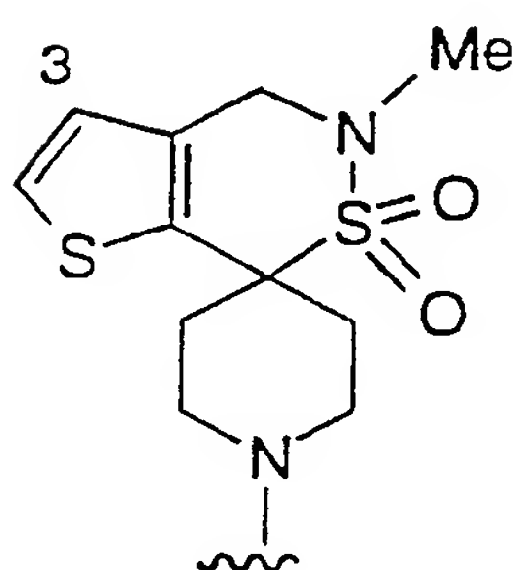
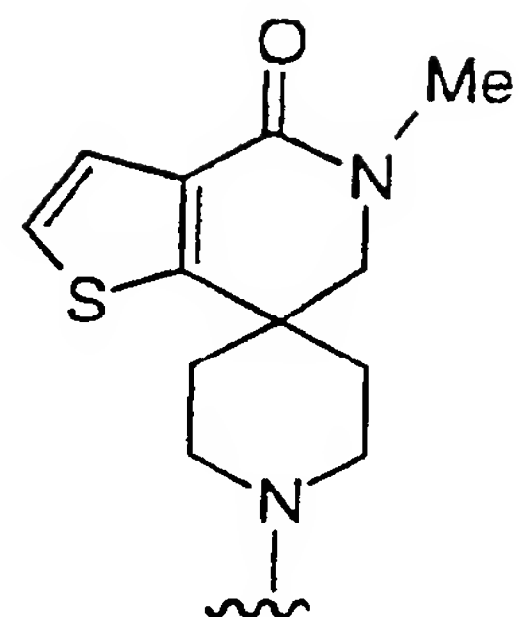
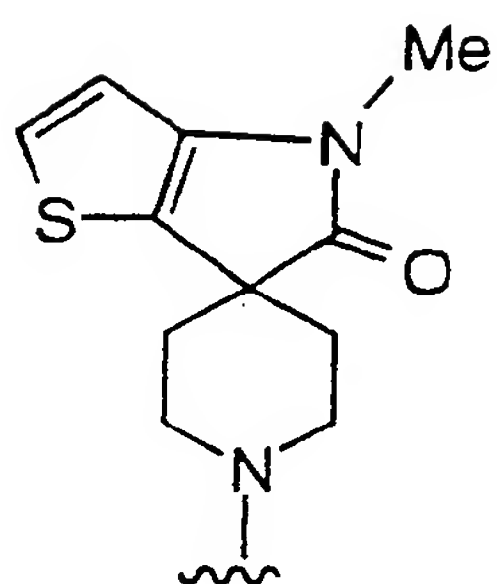
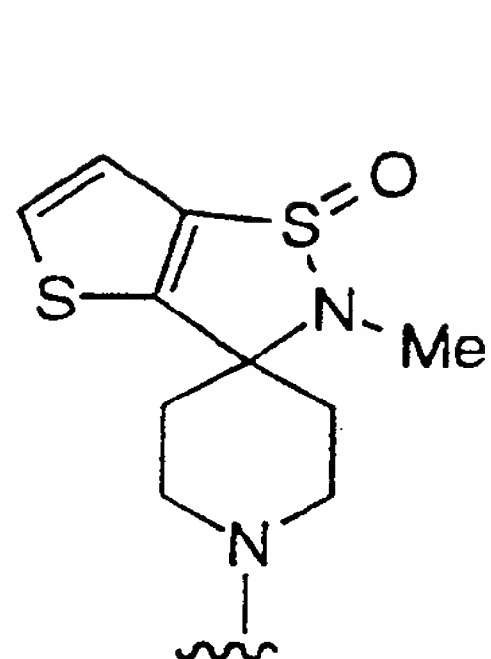


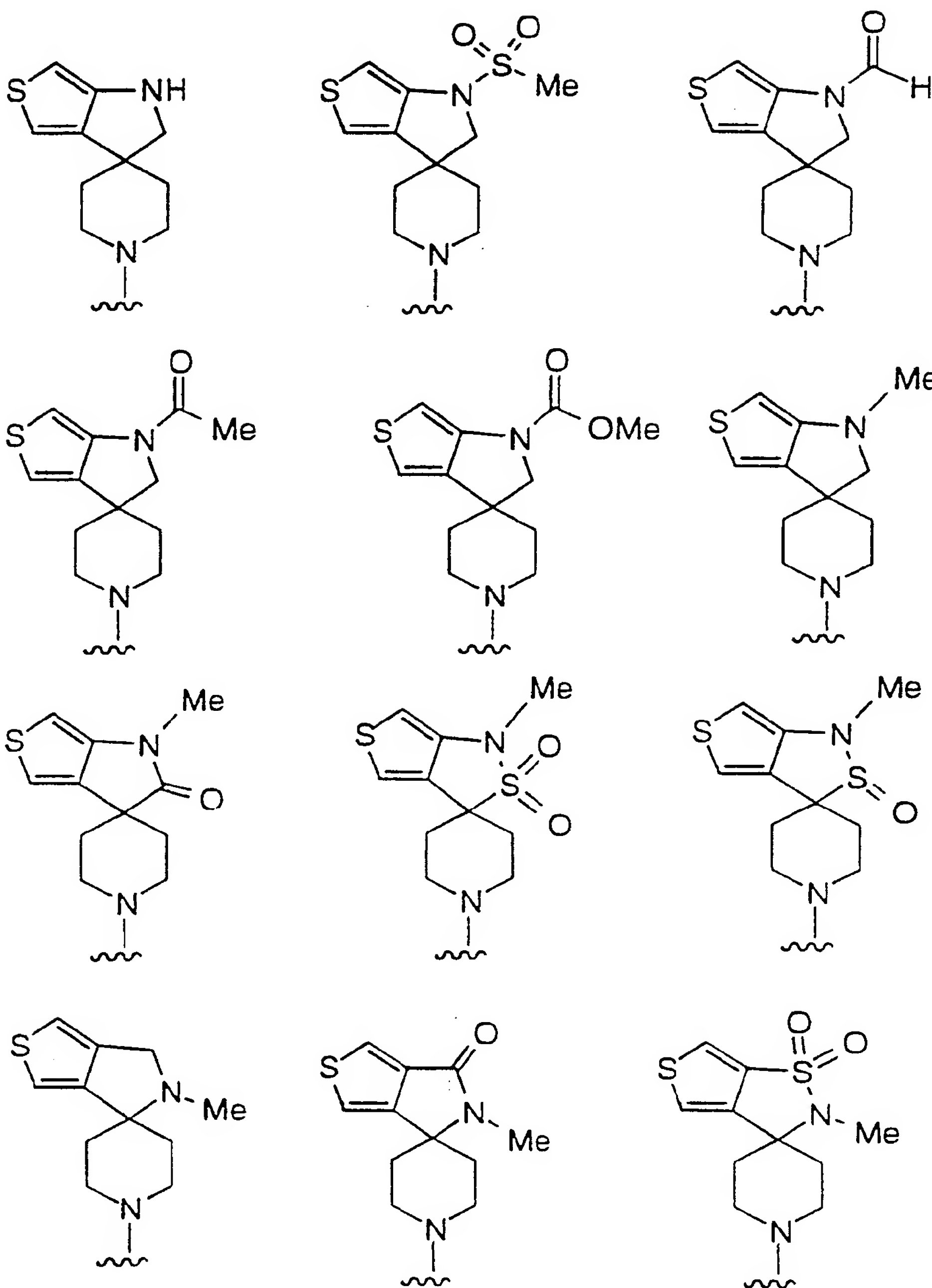


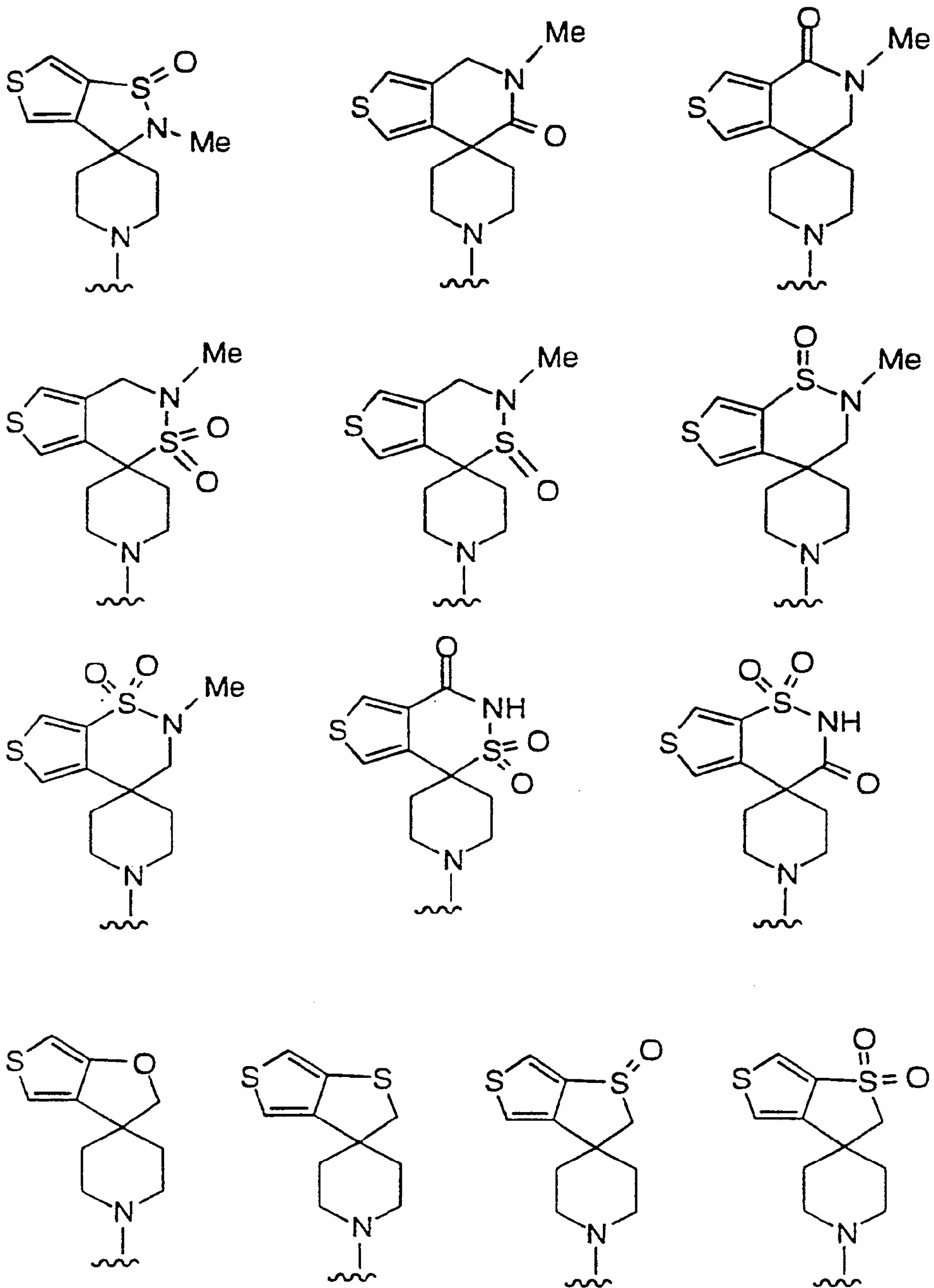


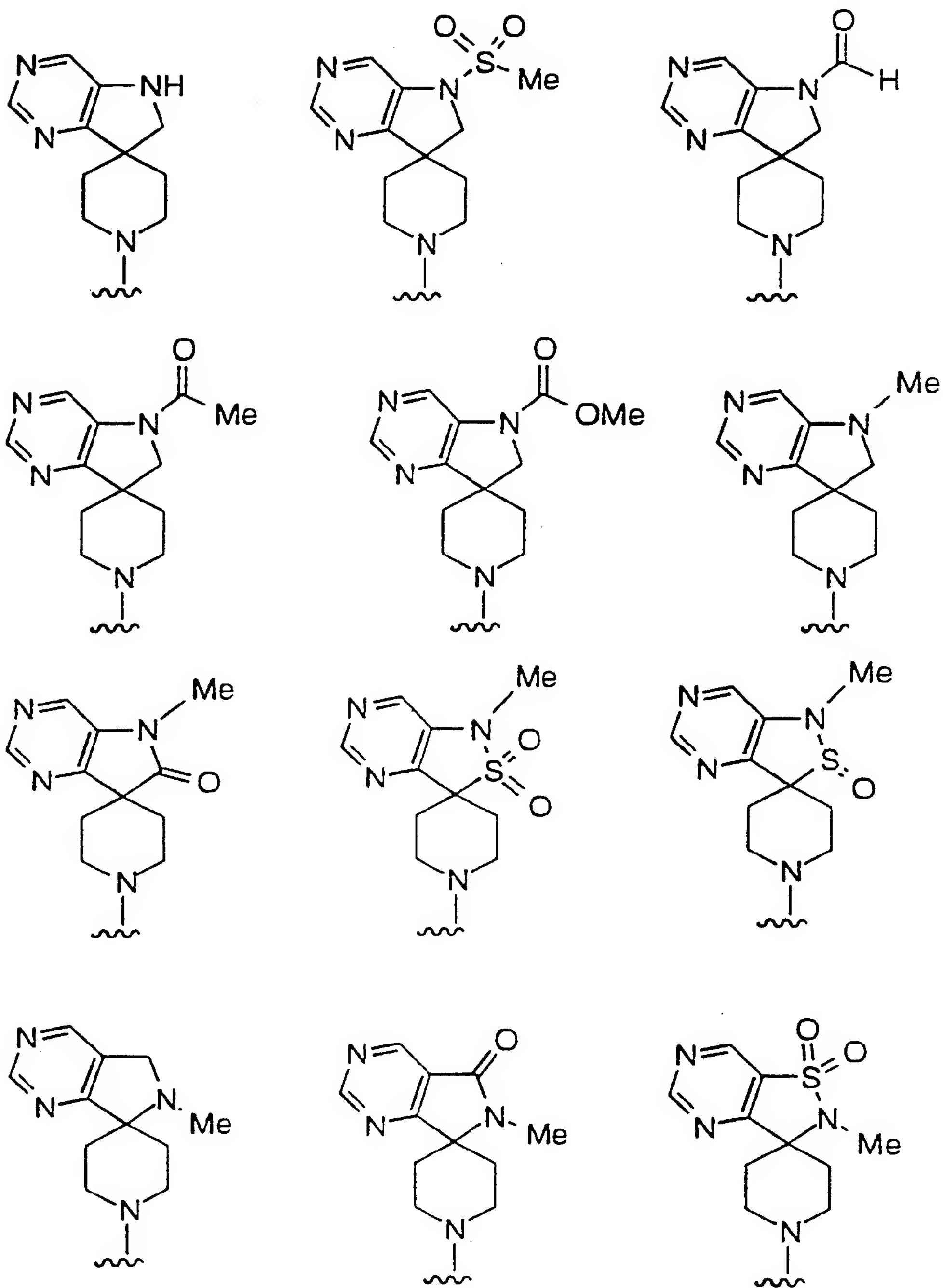


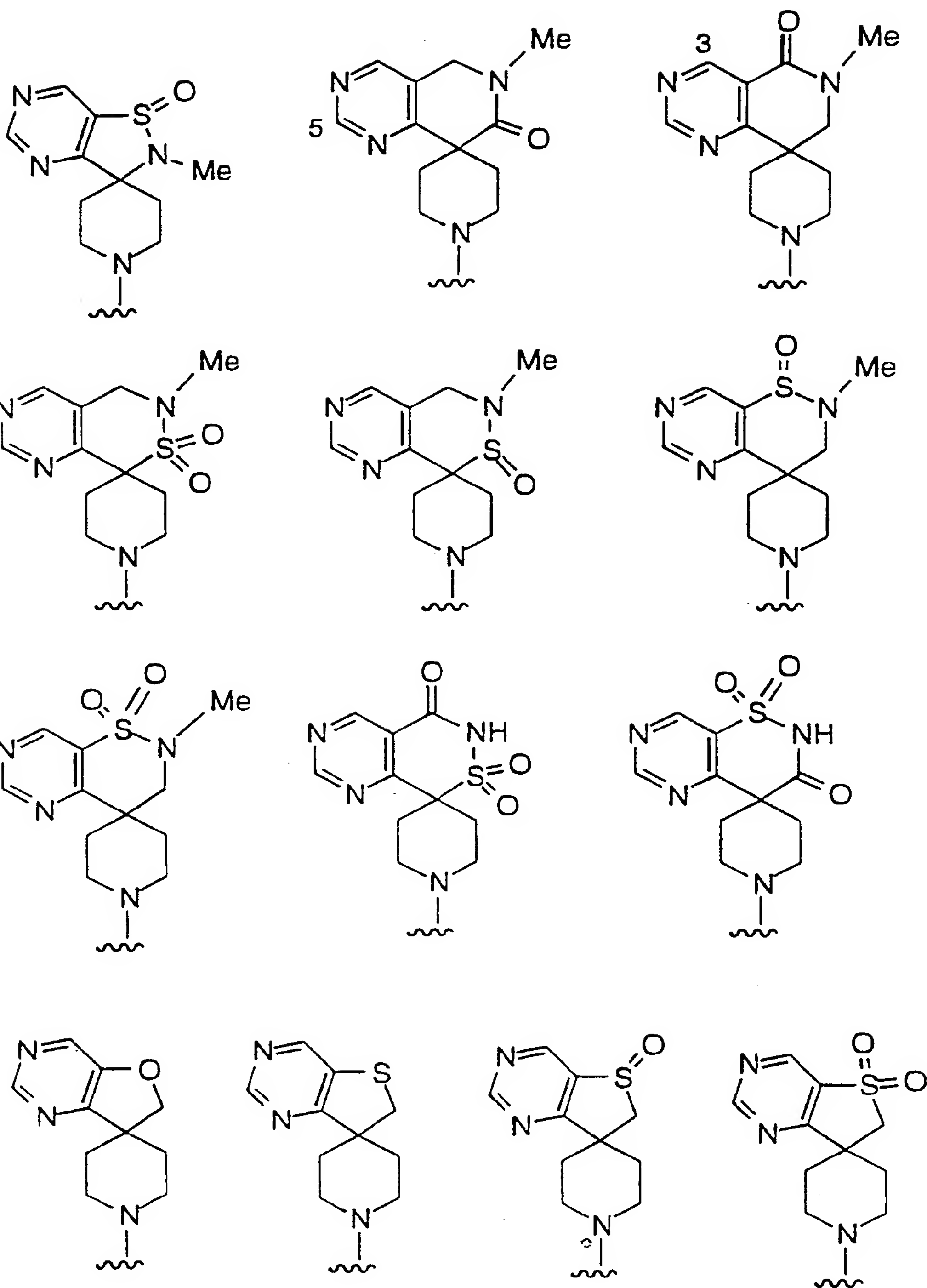






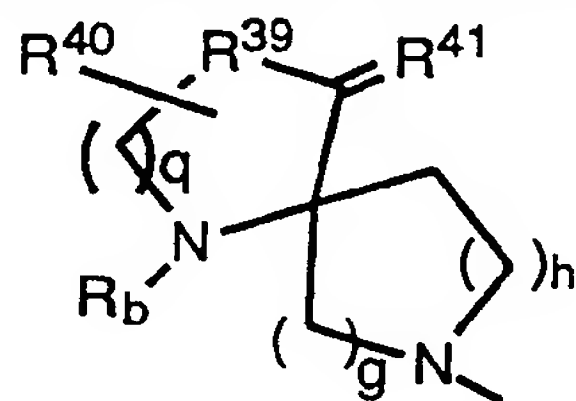




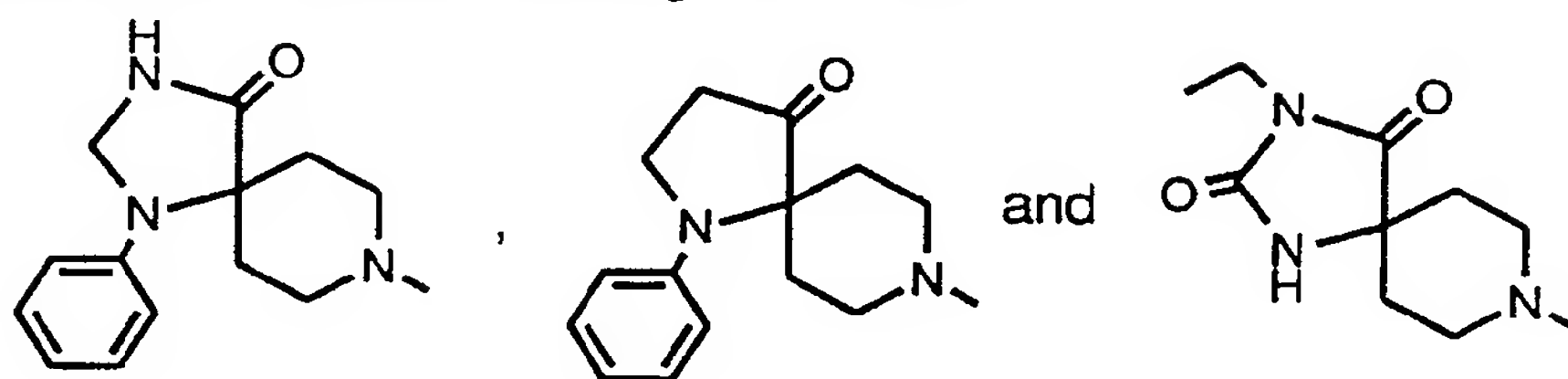


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Preferred definitions of Z having the spirocyclic structure

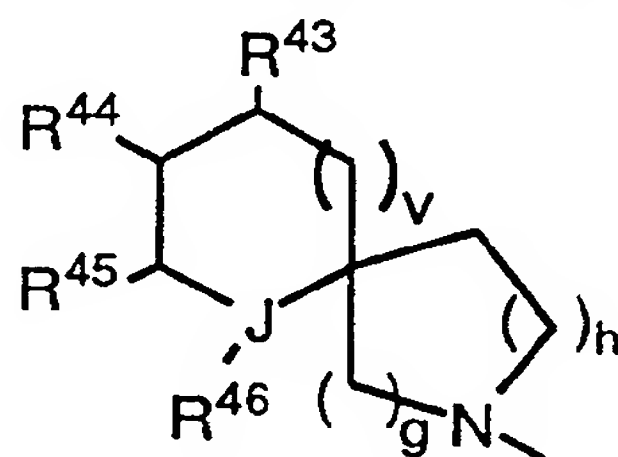


are exemplified by the following structures:

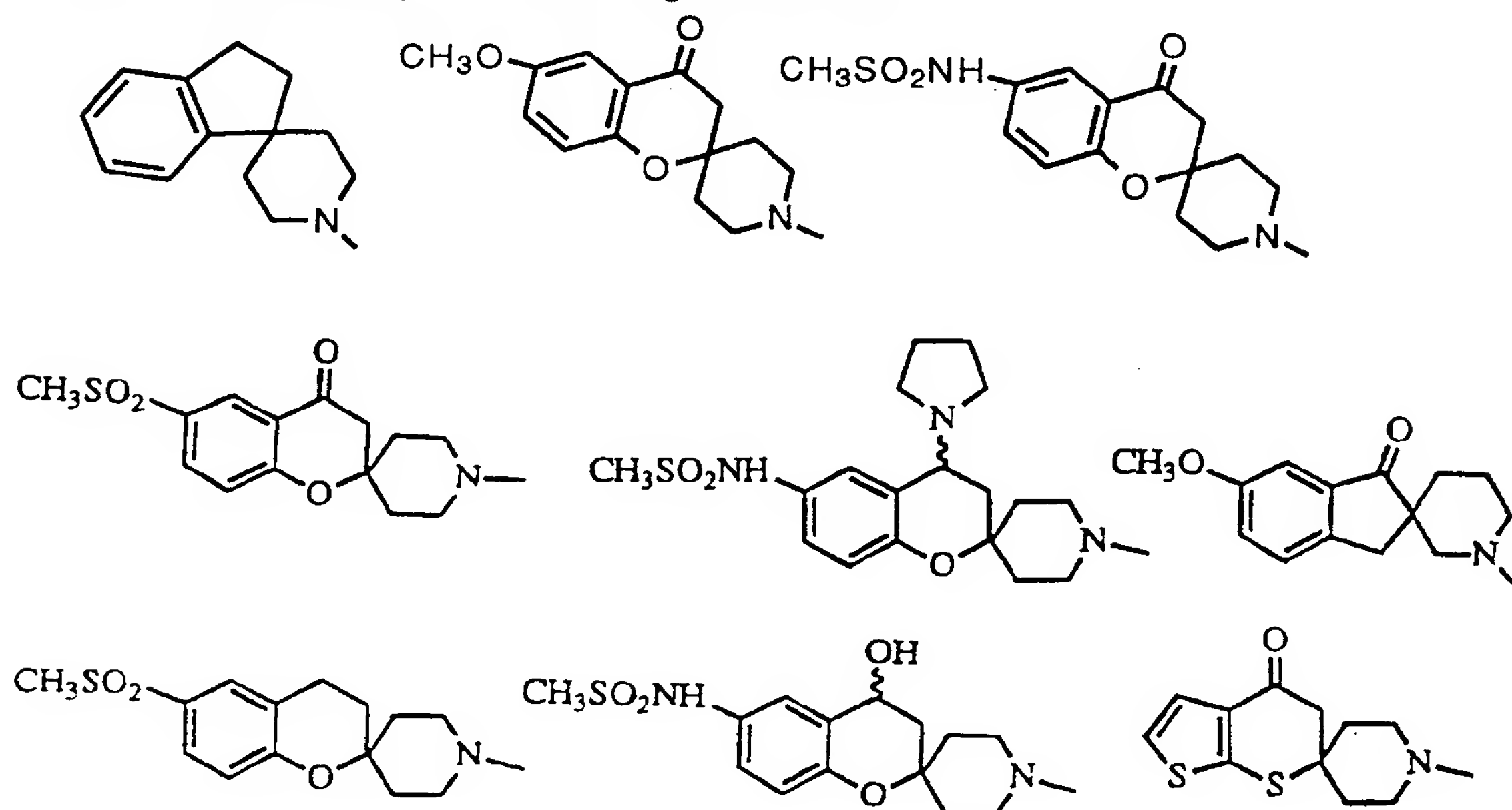


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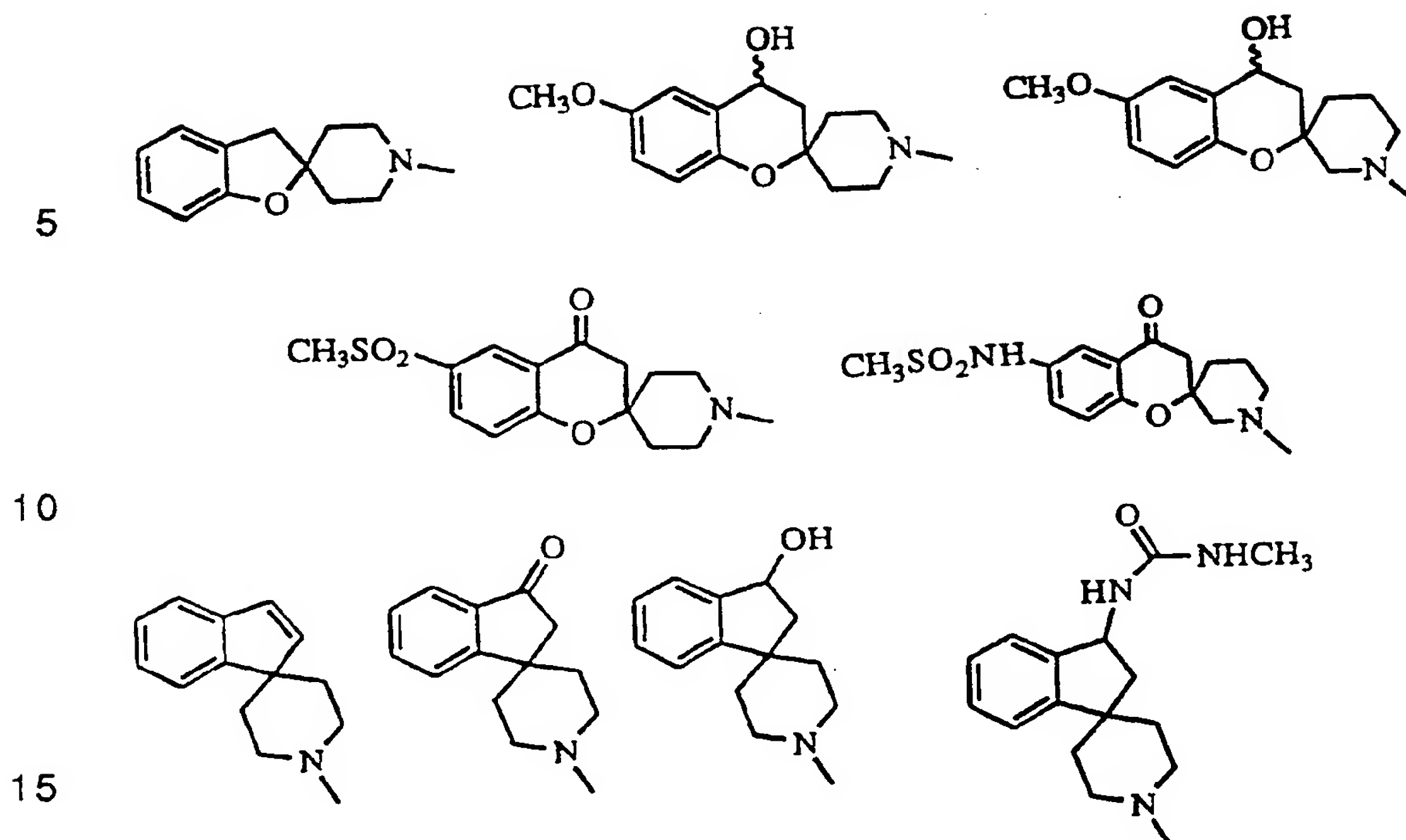
Preferred definitions of Z having the spirocyclic structure



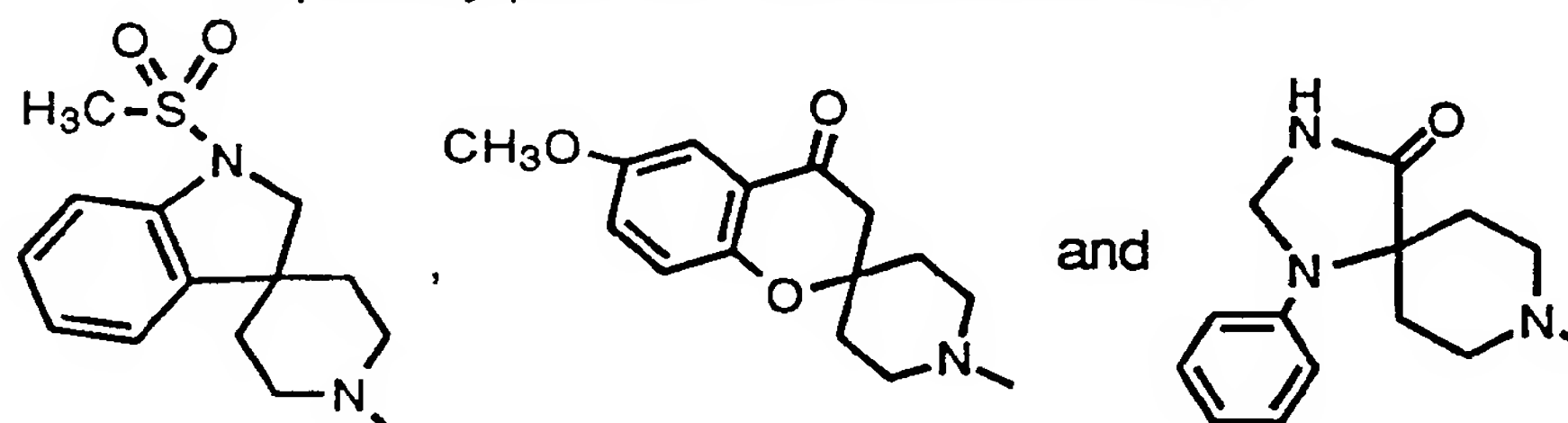
are exemplified by the following structures:



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Especially preferred definitions of Z are:



or any stereoisomer thereof, including any enantiomer, diastereomer, R or S form thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula I in combination with a pharmaceutically acceptable carrier.

The invention also relates to a method for inducing neurokinin antagonism which comprises administering a neurokinin antagonistic effective amount of a compound of formula I to a mammal in need thereof.

The invention also relates to a method for treating chronic airway diseases such as asthma and allergies; inflammatory diseases such as inflammatory bowel disease, psoriasis, fibrositis, osteoarthritis, and rheumatoid arthritis; migraine; central nervous system disorders such as

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emesis, depression, psychosis, dementia, and Alzheimer's disease; Down's syndrome; neuropathy; multiple sclerosis; ophthalmic disorders; conjunctivitis; auto immune disorders; graft rejection; systemic lupus erythematosus; GI disorders such as Crohn's disease and ulcerative colitis; disorders of bladder function; circulatory disorders such as angina; Raynaud's disease; coughing and pain. In particular, the invention also relates to a method of treating asthma which comprises administering to a mammal in need of such treatment an anti-asthma effective amount of a compound of formula I for such purpose.

DETAILED DESCRIPTION OF THE INVENTION

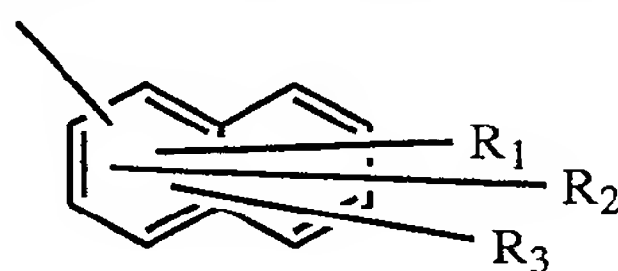
As used herein the term alkyl means a straight or branched, saturated hydrocarbon chain having from 1 to 6 carbon atoms. The number of carbon atoms may be designated. For example, "C₁-C₆ alkyl" represents a straight or branched, saturated hydrocarbon having from 1 to 6 carbon atoms.

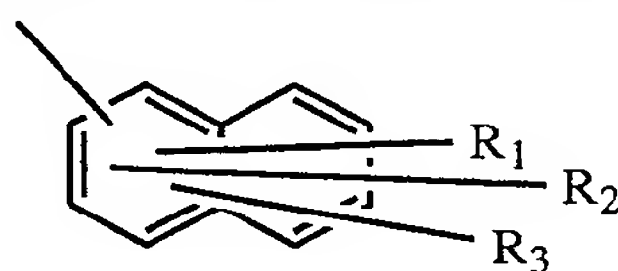
The term C₃-C₆ cycloalkyl means a cycloalkyl having from 3 to 6 carbon atoms, that is cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The term alkenyl means means a straight or branched, saturated alkenyl having from 2 to 6 carbon atoms. The number of carbon atoms may be designated. For example, "C₂-C₆ alkenyl" represents a straight or branched alkenyl having from 1 to 6 carbon atoms.

The term alkynyl means a straight or branched alkynyl having from 2 to 6 carbon atoms. The number of carbon atoms may be designated. For example, "C₂-C₆ alkynyl" represents a straight or branched chain alkynyl having from 2 to 6 carbon atoms.

As used herein, a heavy dark line (**—**) denotes a chemical bond coming above the plane of the page. A dashed line (**----**) denotes a chemical bond coming below the plane of the page.



As used herein, , for example, means that R₁, R₂, and R₃ can be in either of the rings of the above naphthyl moiety.

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Asymmetric centers exist in compounds of formula I of the invention. Accordingly, compounds of formula I include stereoisomers, i.e., enantiomers, diastereomers, endo and exo forms.

5 All such isomeric forms and mixtures thereof are within the scope of the present invention. Unless otherwise indicated, the methods of preparation disclosed herein may result in product distributions which include all possible structural isomers, although it is understood that physiological response may vary according to stereochemical structure. The isomers may be separated by conventional means such as
10 fractional crystallization, preparative plate or column chromatography on silica, alumina, or reversed phase supports or HPLC (high performance liquid chromatography).

Enantiomers may be separated, where appropriate, by derivatization or salt formation with an optically pure reagent, followed
15 by separation by one of the aforementioned methods. Alternatively, enantiomers may be separated by chromatography on a chiral support.

The compounds of formula I can exist in unsolvated as well as solvated forms, including hydrated forms, e.g. the hemihydrate. In general, the solvated forms, with pharmaceutically acceptable solvents
20 such as water, ethanol, and the like are equivalent to the unsolvated forms for the purposes of the invention.

Those compounds of formula I which contain a basic group such as $-CH_2NH_2$, form pharmaceutically acceptable salts. The preferred pharmaceutically acceptable salts are nontoxic acid addition salts
25 formed by adding to a suitable compound of the invention about a stoichiometric amount of a mineral acid, such as HCl, HBr, H_2SO_4 or H_3PO_4 or of an organic acid such as acetic, propionic, valeric, oleic, palmitic, stearic, lauric, benzoic, lactic, para-toluenesulfonic, methanesulfonic, citric, maleic, fumaric, succinic and the like,
30 respectively.

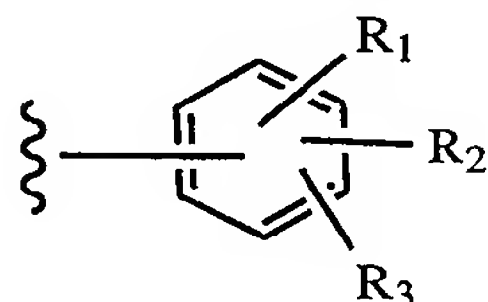
GENERAL METHODS OF PREPARATION

The compounds of this invention may be prepared by one of the following general methods. As used herein RT means room
35 temperature. Unless otherwise indicated, variables in the structural formulas below are as defined above. Starting materials and reagents

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used in the methods and examples below, are known or may be prepared according to known methods.

As used herein the term "substituted phenyl" means



wherein R₁, R₂, and R₃ are as described herein.

5 "Substituted" means substituted by R₁, R₂, and/or R₃ as described herein.

"Aryl" means phenyl, naphthyl, indenyl, tetrahydronaphthyl, indanyl, anthracenyl or fluorenyl.

"Halogeno" refers to fluoro, chloro, bromo or iodo atoms.

10 "Heterocycloalkyl" refers to 4- to 6-membered rings comprising 1 to 3 heteroatoms independently selected from the group consisting of -O-, -S- and -N(R⁶)-, with the remaining ring members being carbon. Examples of heterocycloalkyl rings are tetrahydrofuranyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl and piperazinyl.

15 "Heteroaryl" refers to 5- to 10-membered single or benzofused aromatic rings comprising 1 to 3 heteroatoms independently selected from the group consisting of -O-, -S- and -N=. Examples of single-ring heteroaryl groups are pyridyl, isoxazolyl, oxadiazolyl, furanyl, pyrrolyl, thienyl, imidazolyl, pyrazolyl, tetrazolyl, thiazolyl, thiadiazolyl, pyrazinyl, pyrimidinyl, pyridazinyl and triazolyl. Examples of benzofused
20 heteroaryl groups are quinolinyl, thianaphthenyl (i.e., benzothienyl) and benzofurazanyl. N-oxides of nitrogen-containing heteroaryl groups are also included. All positional isomers are contemplated, e.g., 1-pyridyl, 2-pyridyl, 3-pyridyl and 4-pyridyl.

25 Where R² and R³ substituents form a ring and additional heteroatoms are present, the rings do not include adjacent oxygen and/or sulfur atoms or three adjacent heteroatoms. Typical rings so formed are morpholinyl, piperazinyl and piperidinyl.

As used herein, the term "BOC" means t-butoxycarbonyl.

30 As used herein, the term "Ph" means phenyl.

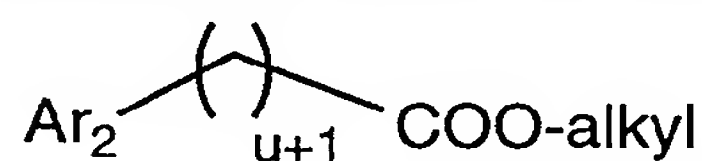
As used herein, the term "parallel synthesis" means the preparation of individual chemical compounds as one of a batch of, for instance, 20, 30, or even 100 identical reactions on usually a single

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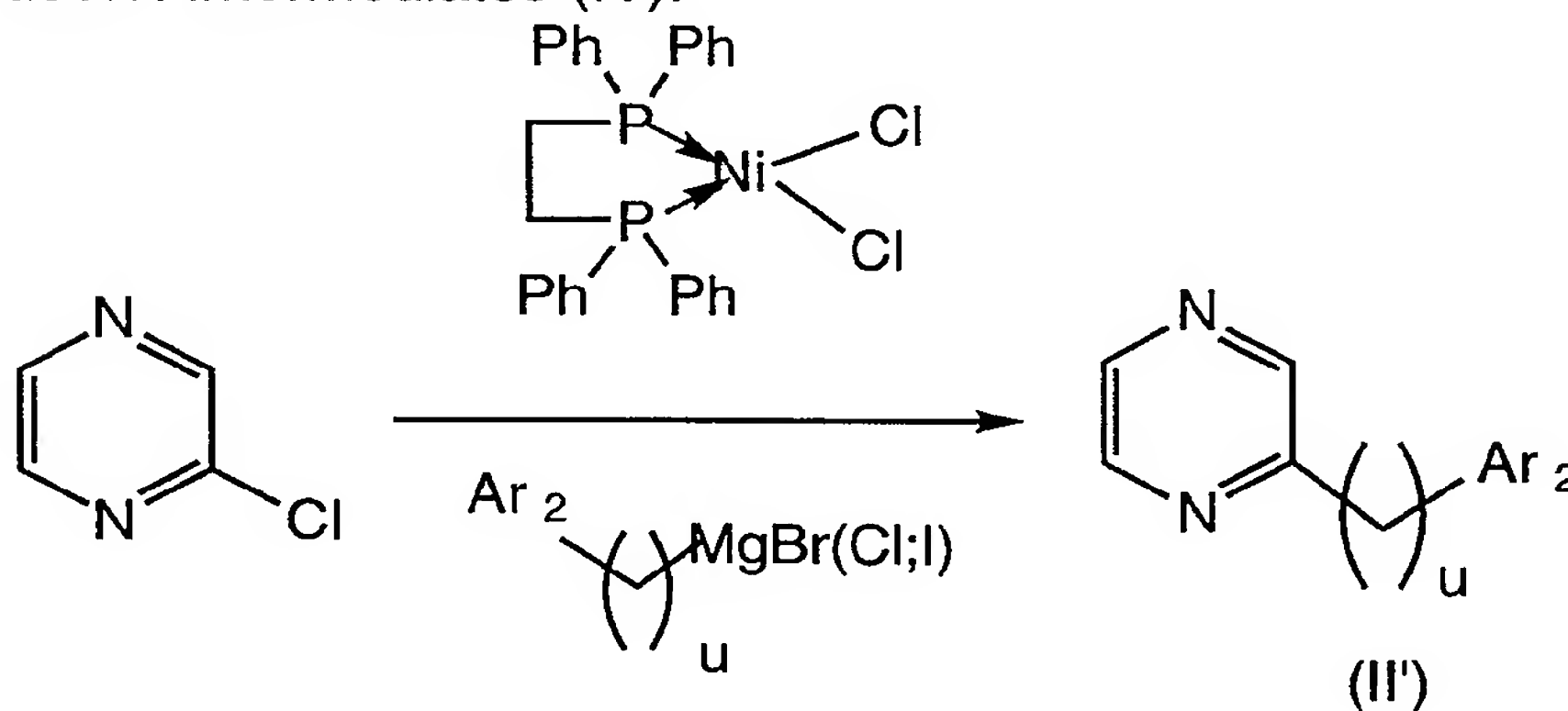
substrate but using a different reagent in each vessel. Such reagents are always of the same general class- in this case, either carboxylic acids or organic amines in any set of parallel reactions. The conditions used for each reaction are identical to those described in the examples ,
 5 except that a simplified work-up is employed, generally a simple wash either with acid or base if appropriate, then water. The presence of the product is detected by thin layer chromatography (TLC) using known products as representative standards. Further characterization by combination HPLC/MS is generally performed. No further purification is
 10 performed on these materials before they are submitted to biological assays.

As used herein, each R_C and $R_{C'}$ is independently selected from the group consisting of H, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, unsubstituted or substituted phenyl, and unsubstituted or substituted
 15 benzyl,

The starting materials in the methods below are either known or can be prepared in accordance with known methods. In particular, the following compounds are either known or can be prepared in accordance with known methods: the diamine A, the compounds of
 20 formulas A, VI, VIII, X, XI, XIV, XVIII, XIX, XXa, A', XXV, and Z-H, as well as esters of formula XI, and compounds of formula

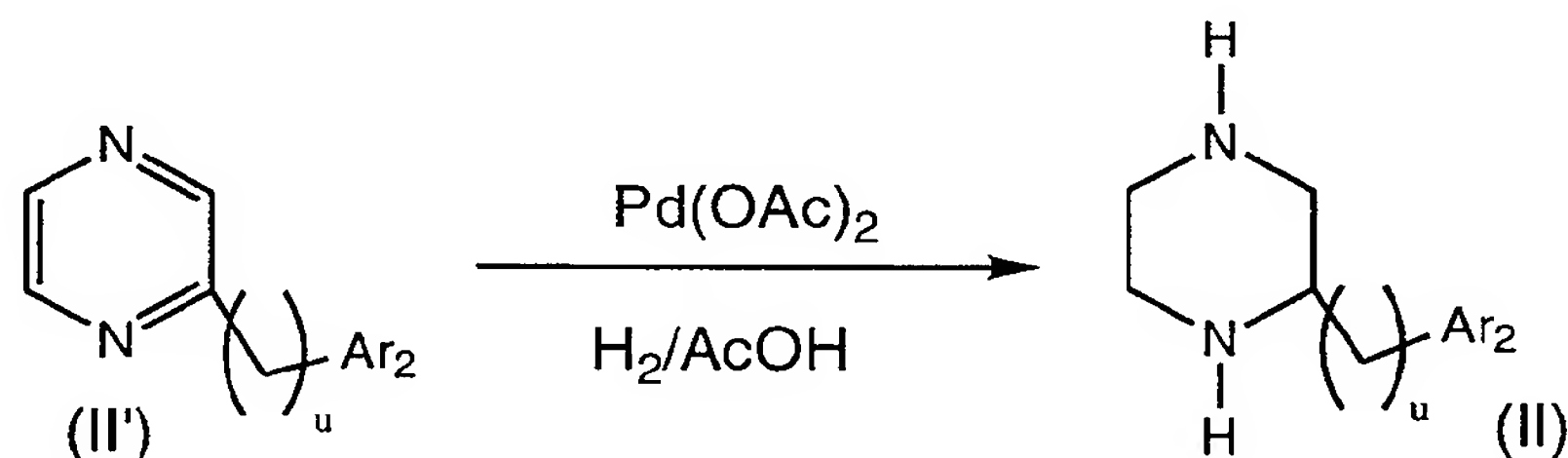


Method 1. If the group Ar_2 is an aromatic group with no I or Br substituents, then the following method may be used to prepare the
 25 useful intermediates (IV):



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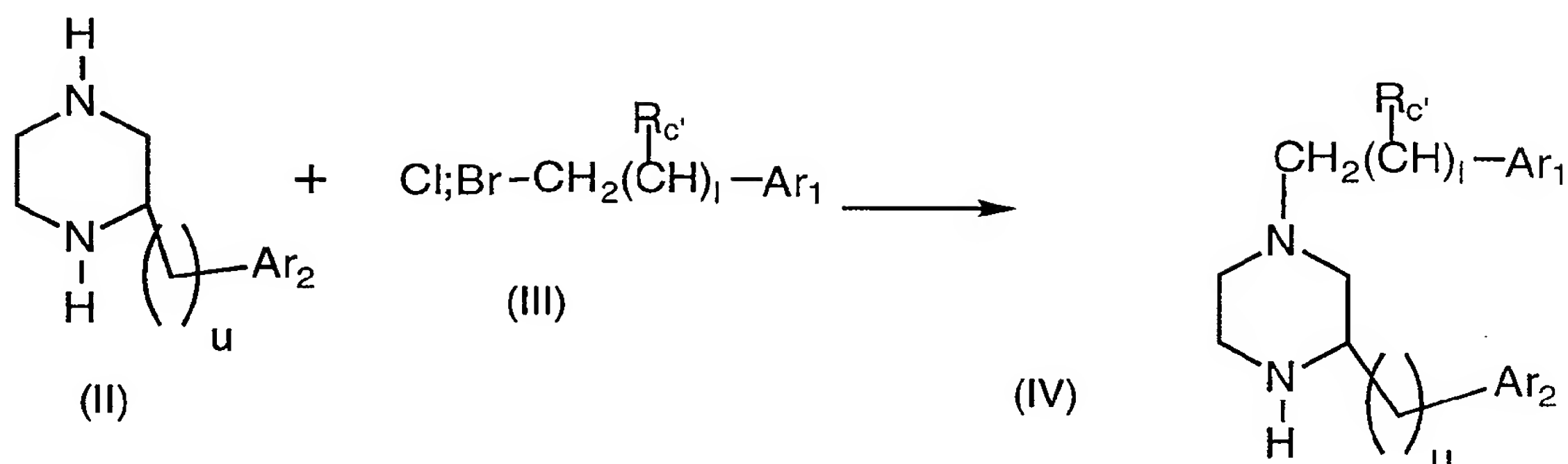
Transition metal catalyzed coupling of 2-chloropyrazine with an aromatic Grignard reagent in a dry, ether solvent, such as THF, yields the aryl-substituted pyrazine of formula II'. The catalyst shown, [1,2-bis-(diphenylphosphino)ethane]nickel^{II} chloride, is a preferred reagent for this transformation. Where Ar₂ has no halo substituents, reduction of a compound of formula II' by catalytic hydrogenation, using, for instance, palladium acetate, preferably in acetic acid solvent, results in preferential reduction of the pyrazine ring, leaving the aromatic ring unreduced, that is, it results in a compound of formula II. Similarly, 10% Pd on charcoal (Pd-C) can be used in an alcohol solvent, preferably methanol, with or without the addition of a small quantity (1 to 5 equivalents) of acetic acid. Reaction times of about 1 to 24 hours generally suffice for this reaction, which is preferentially run at room temperature or slightly above (up to about 50°C) and using from 1 to about 6 atmospheres pressure of hydrogen.



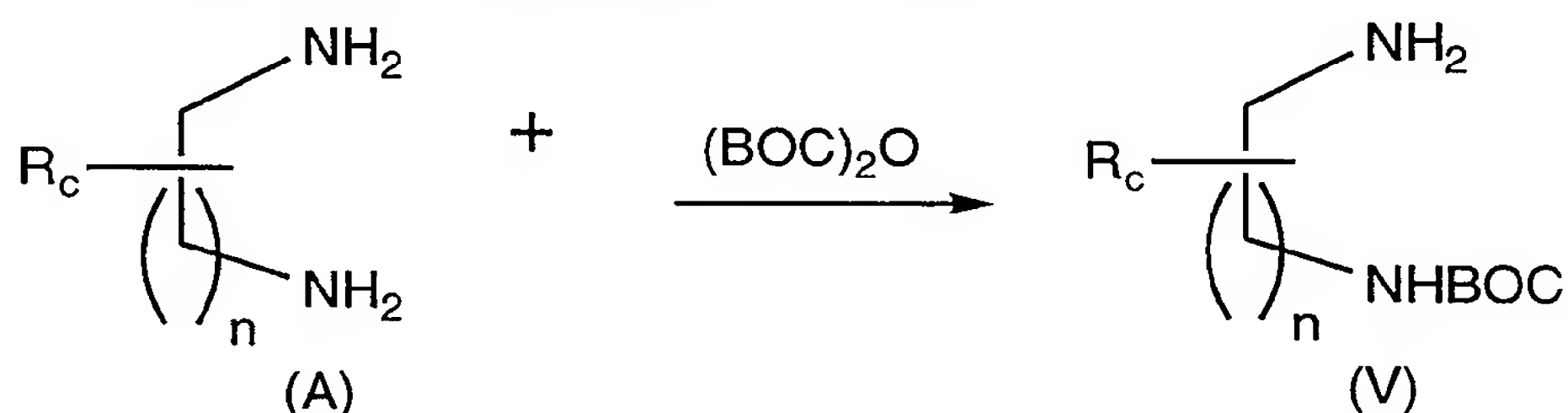
The intermediate of formula II may also be prepared from a compound of formula II', even if the group Ar₂ contains halogen atoms, by reduction using a strong hydride ion donor, preferably lithium aluminum hydride (LAH) or diisobutyl aluminum hydride (DIBAL-H) in an ether solvent, such as ether, THF or dimethoxyethane (DME).

Selective alkylation of a compound of formula II is possible using low temperature conditions. Thus, reacting a compound of formula II with a substituted aryl-alkyl halide of formula III where I is 0 to 2, results in the formation of the 4-substituted derivative of formula IV. Suitable conditions include use of a halogenated solvent, such as CH₂Cl₂, at low temperature. Suitable temperatures are from -78°C initially, allowing the reaction mixture to warm gradually to RT if the reaction is not completed after several hours. The reaction is catalyzed by the addition of an equivalent amount of an organic base, such as triethylamine and diisopropylethylamine (Hünig's base).

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Method 2. If the group Ar_2 contains one or more halogen atoms on an aromatic ring and the other groups are as in Method 1, then an alternate route to a compound of formula IV is preferred. In addition, this method can be used to prepare compounds in which l is from 0 to 2. Mono-protection of the diamine of formula (A), preferably with BOC anhydride, or other agents known to introduce the t-butyloxycarbonyl protecting group, in an alcohol solvent, such as methanol, preferably at about -10°C , produces a compound of formula V.



10

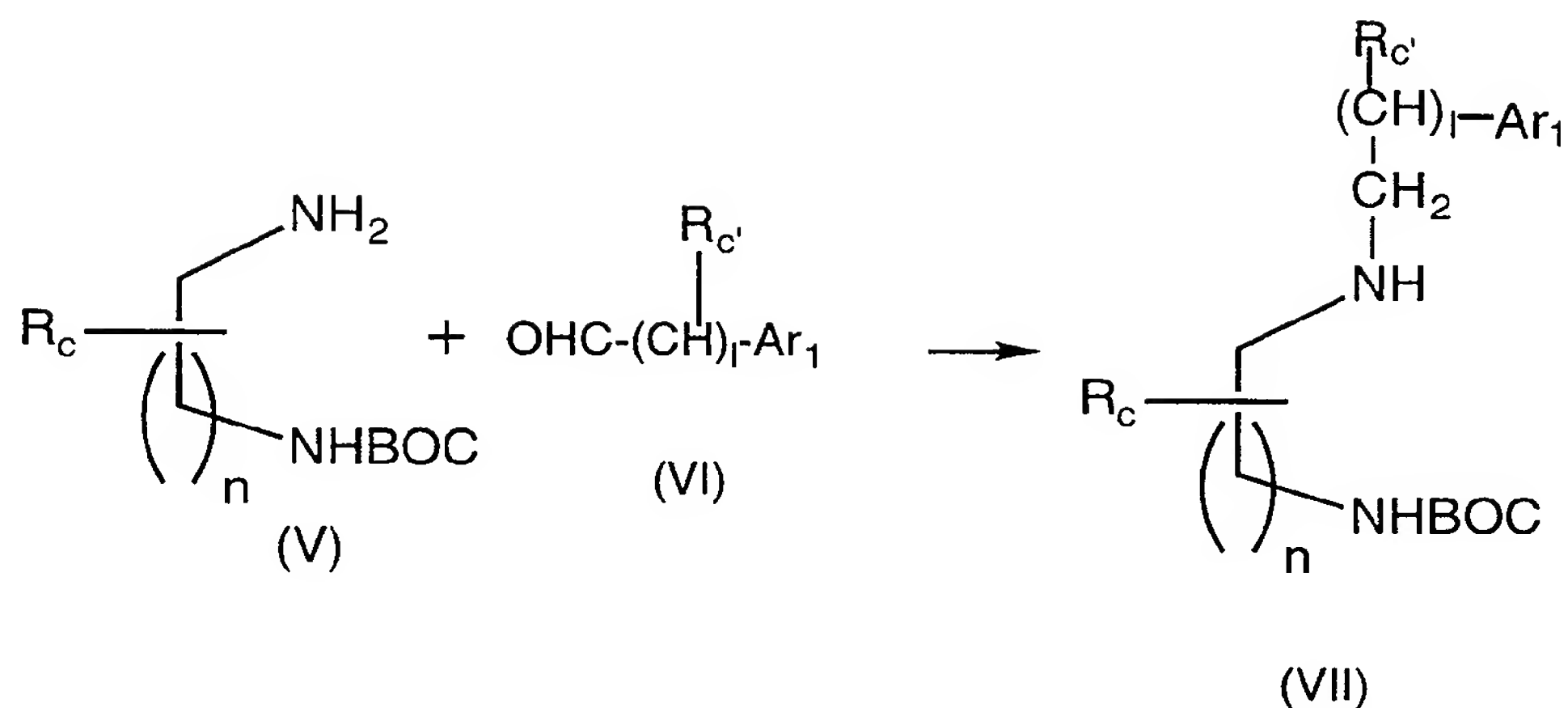
These compounds are used to perform a reductive amination reaction with the aldehyde of formula VI to produce an amine of formula VII. (In structures (A), (V), (VII), and (IX) herein, R_c can be bound to any position between the two nitrogens. In cyclic structures like (IVA) below, R_c can be bound to any available cyclic position that is occupied by carbon, and that is between the two nitrogens.)

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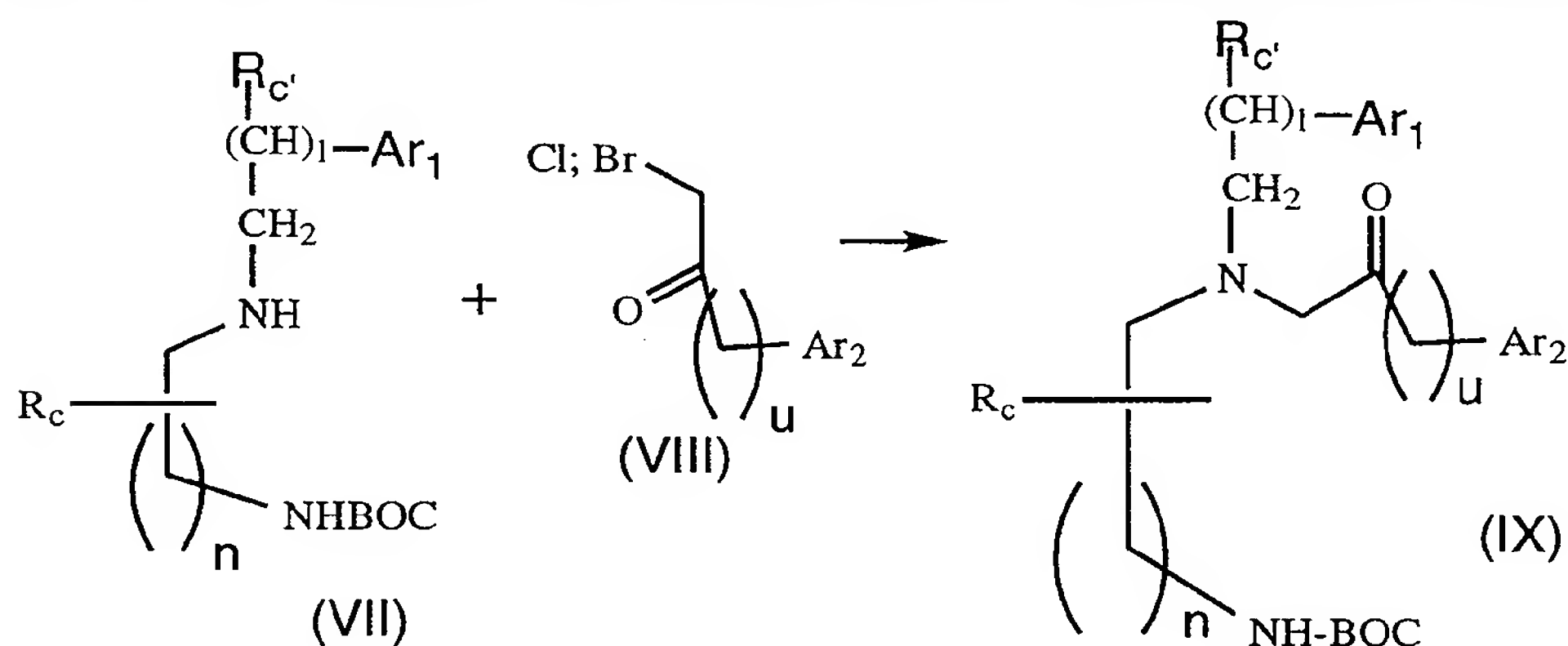
Suitable conditions for this type of reaction include the use of an alcohol solvent, preferably methanol, or 2,2,2-trifluoroethanol, made slightly acidic with a weak organic acid, such as acetic acid, and a reducing agent known to favor reductive amination reactions, preferably sodium cyanoborohydride, NaBH_3CN .

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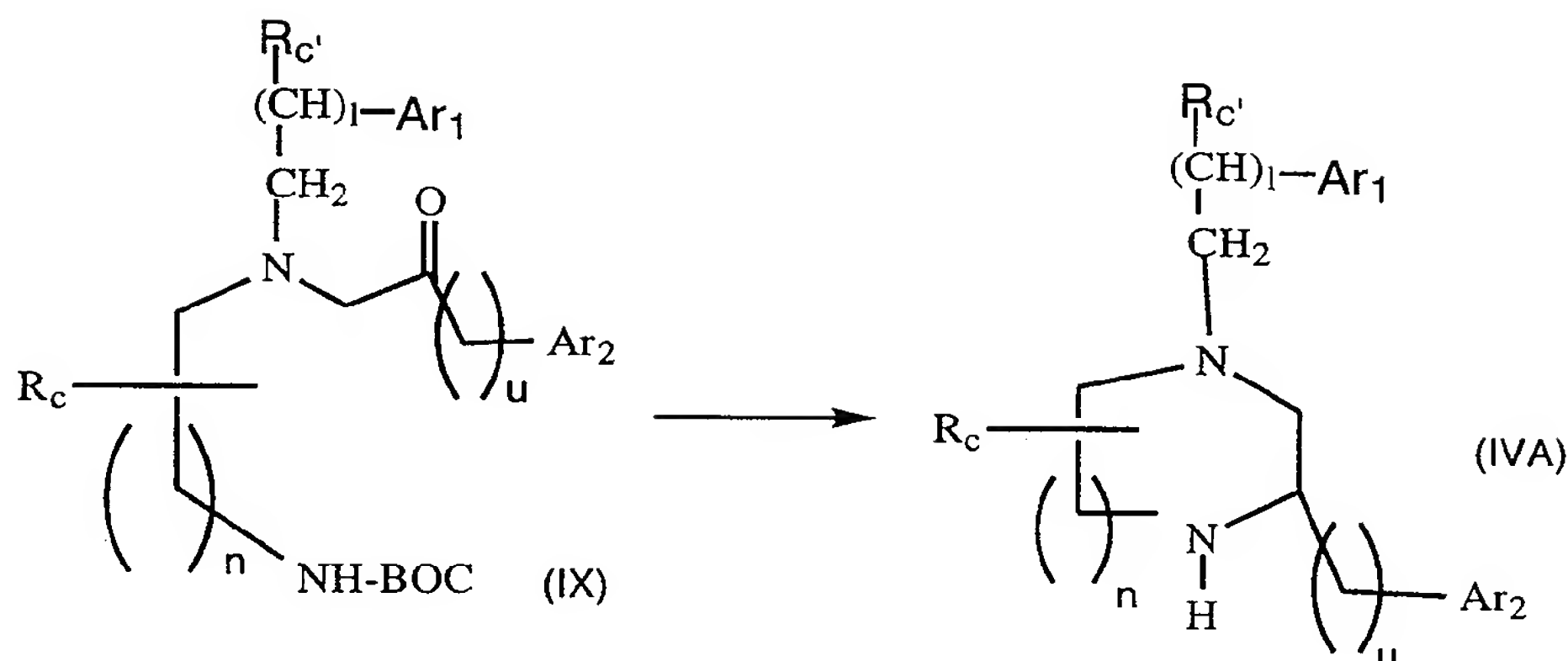
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Reaction of a compound of formula VII with an α -haloketone of formula VIII, in which Ar₂ preferably represents a halogenated aromatic ring, but may be any of the claimed aromatic rings, in the presence of an organic base, such as di-isopropylethylamine, also known as Hünig's Base, in an ether solvent, such as THF, results in the formation of the intermediates of formula IX.

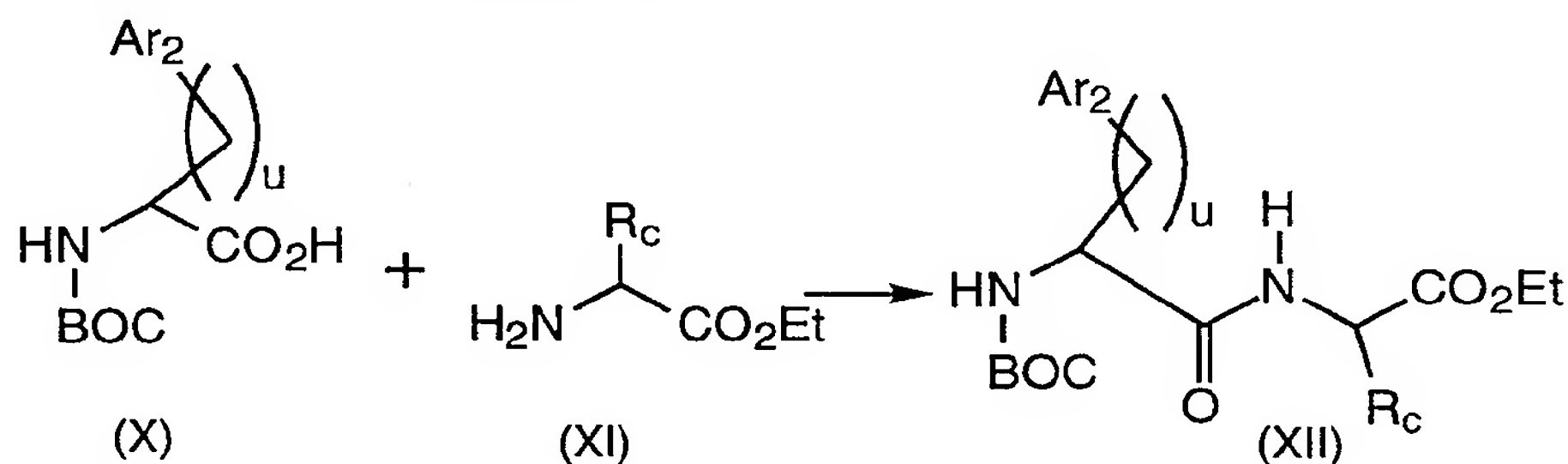


Removal of the BOC protecting group using a suitable acidic catalyst, such as trifluoroacetic acid, followed by an intramolecular reductive amination, under conditions such as those described above for the preparation of a compound of formula VII, leads to the formation of compounds of formula IVA.



Method 3. An alternate route to compounds of the invention in which *l* is 0 to 2 is as follows. Standard coupling of an N-protected amino acid of formula X, wherein *Ar*₂ is as described above, with an amino acid

- 5 ester derivative $\text{H}_2\text{N}-\text{CH}(\text{R}_c)-\text{COOR}'$ (*R'* is C₂-C₄ alkyl, preferably, the ethyl ester of formula XI, .Et in the formulas herein means ethyl), produces a dipeptide of formula XII. A suitable protecting group is BOC, although many others may also be used. Other esters of the amino acid may also be used. Standard coupling techniques may be applied, an
- 10 example being the use of N-hydroxybenztriazole (HOBT) and a water-soluble carbodiimide, such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (DEC), in a non-hydroxylic solvent such as CH₂Cl₂, DMF or a mixture of the two foregoing solvents. The reaction is run, preferably, at or below RT, and takes from 1 to 40 hours for completion,
- 15 depending upon the substrates.

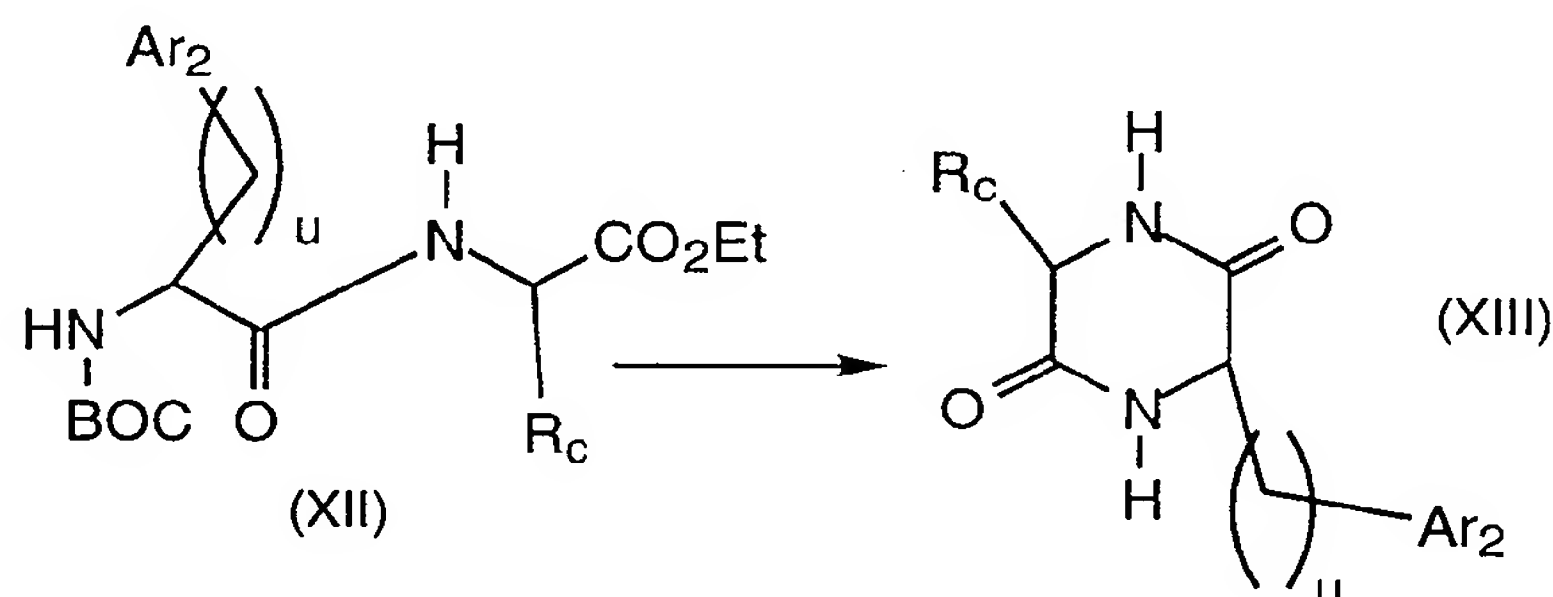


Removal of the protecting group under standard conditions, followed by treatment of the product with a base results in cyclization to the diketopiperazine of formula XIII. Suitable conditions for removal of

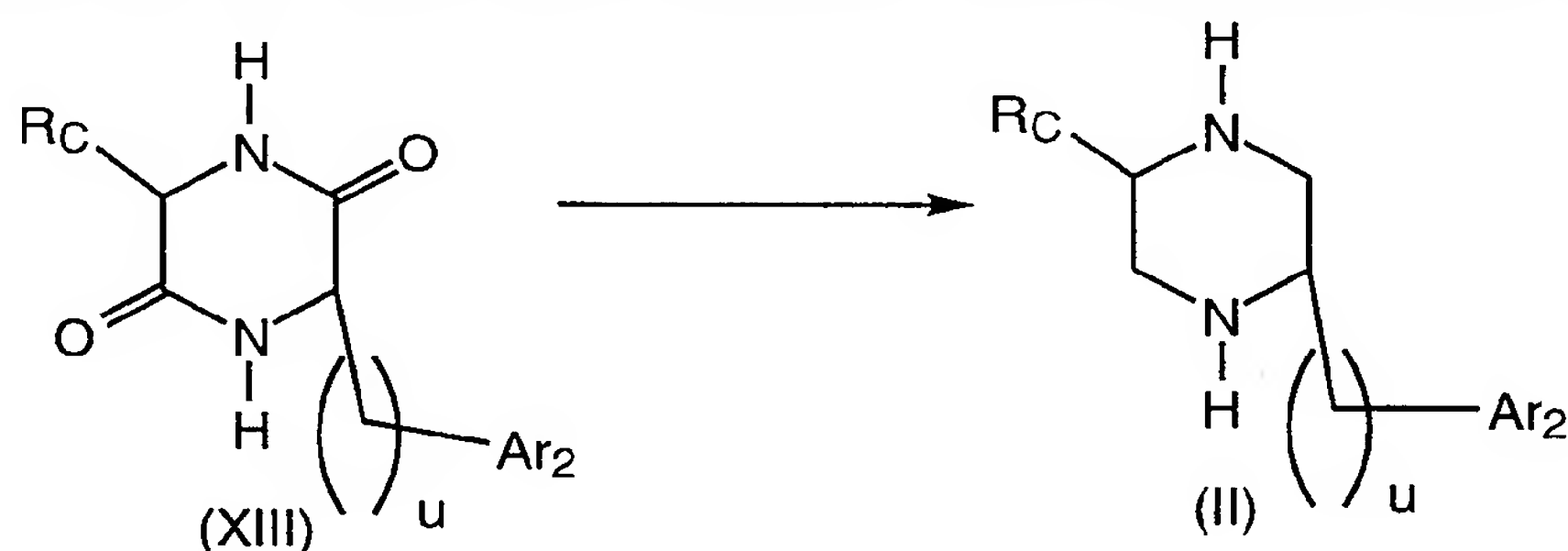
20 the exemplified BOC group are well known in the art and include

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catalysis by trifluoroacetic acid (TFA). A suitable base for cyclization is the alkali metal salt of an alcohol in the alcohol itself used as solvent. For example, a solution of sodium ethoxide in ethanol may be used. The temperature is preferably around RT but may be slightly above or below, in the range 0°C to about 40°C. The reaction is generally complete within a few hours. Suitable reaction times are from 1 to 24 hours.

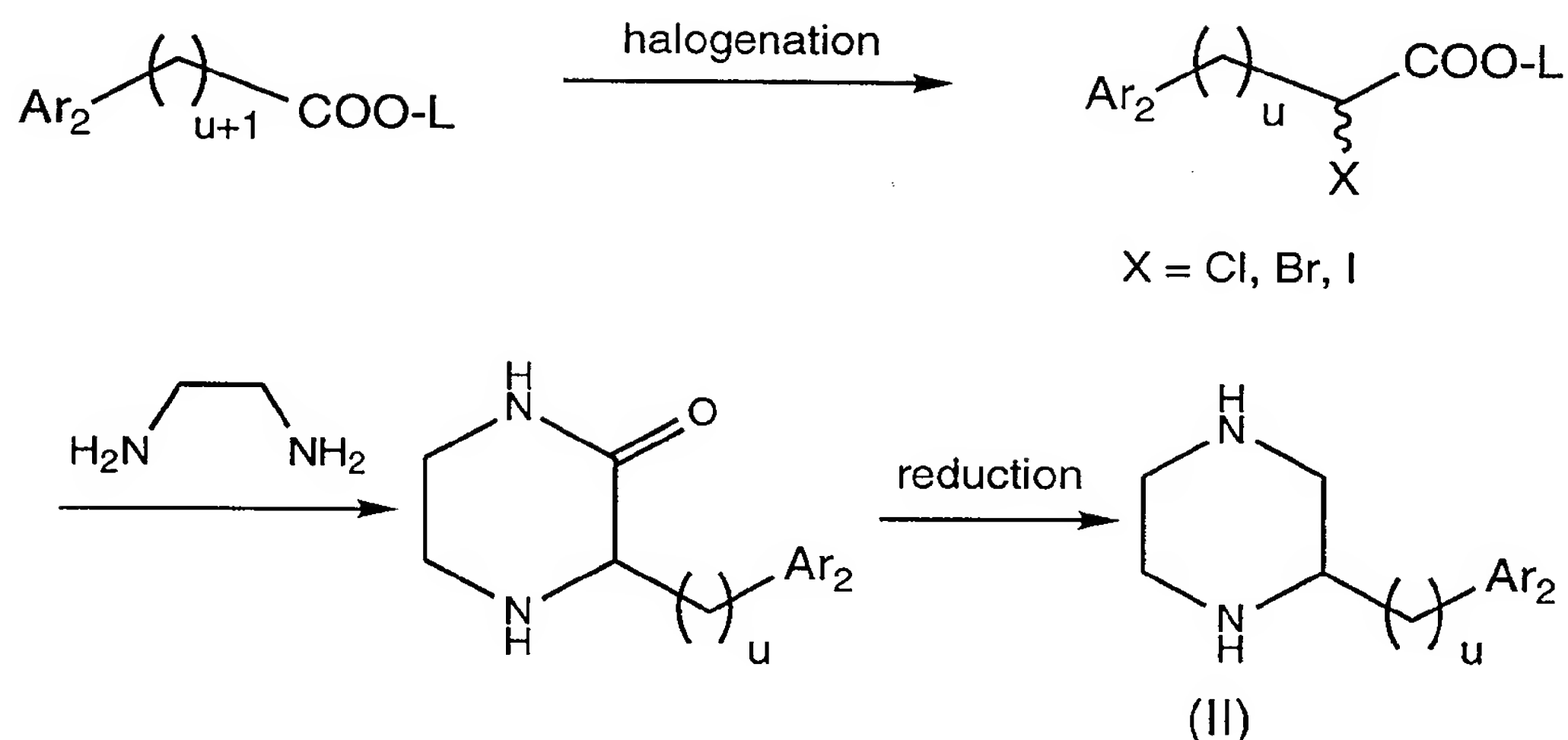


Reduction of the diketopiperazine of formula XIII to a compound of formula II may be accomplished preferentially with a strong hydride reducing agent, such as LAH or a solution of sodium bis(2-methoxyethoxy)aluminum hydride in toluene (also known as Red-Al®), or the $\text{BH}_3 \cdot \text{S}(\text{CH}_3)_2$ complex. Suitable solvents for this reaction are DME and other higher boiling ethers since the reaction is run at elevated temperatures, from about 50°C to about 110°C, preferably about 90°C.



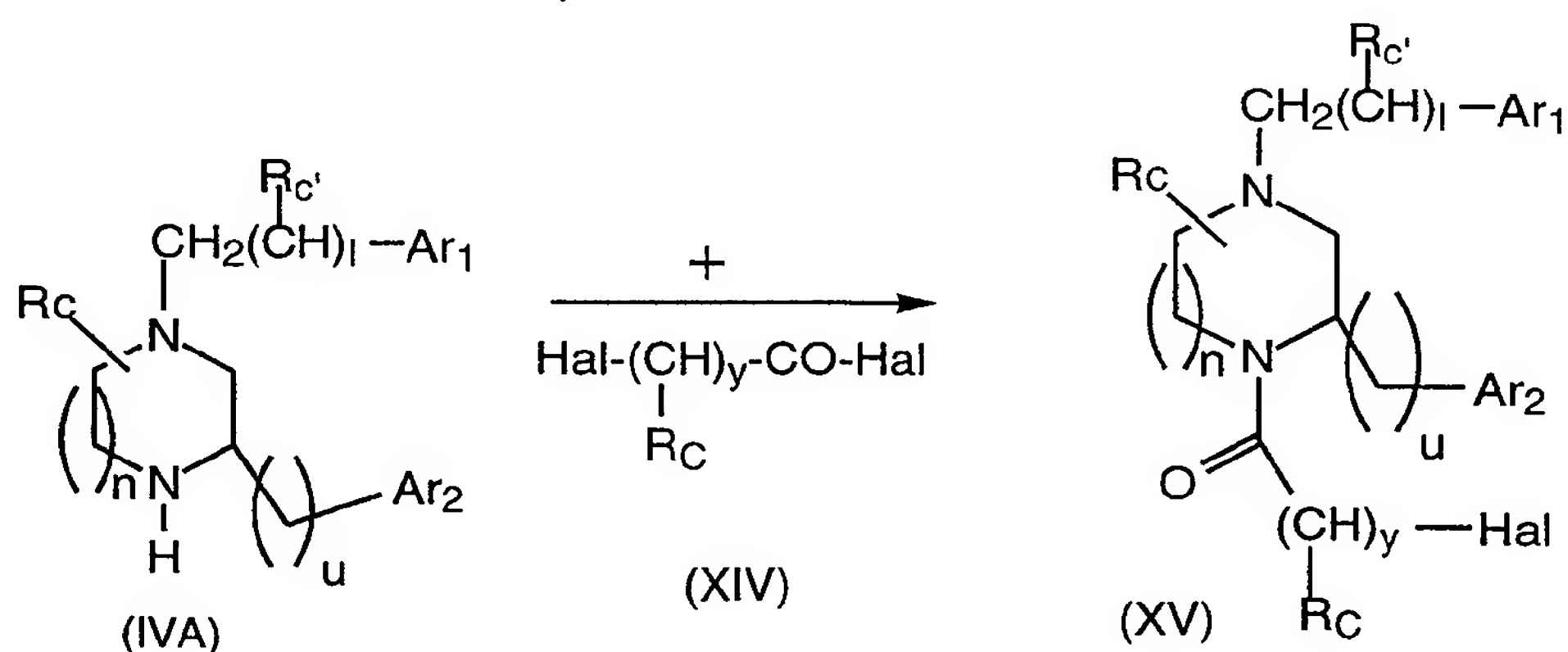
Alternatively, a compound of formula of II may be prepared by the scheme shown below (J. Med. Chem., 9, 191 (1966)). As used herein L is any readily available ester residue such as C_1 - C_7 alkyl, more preferably methyl or ethyl.

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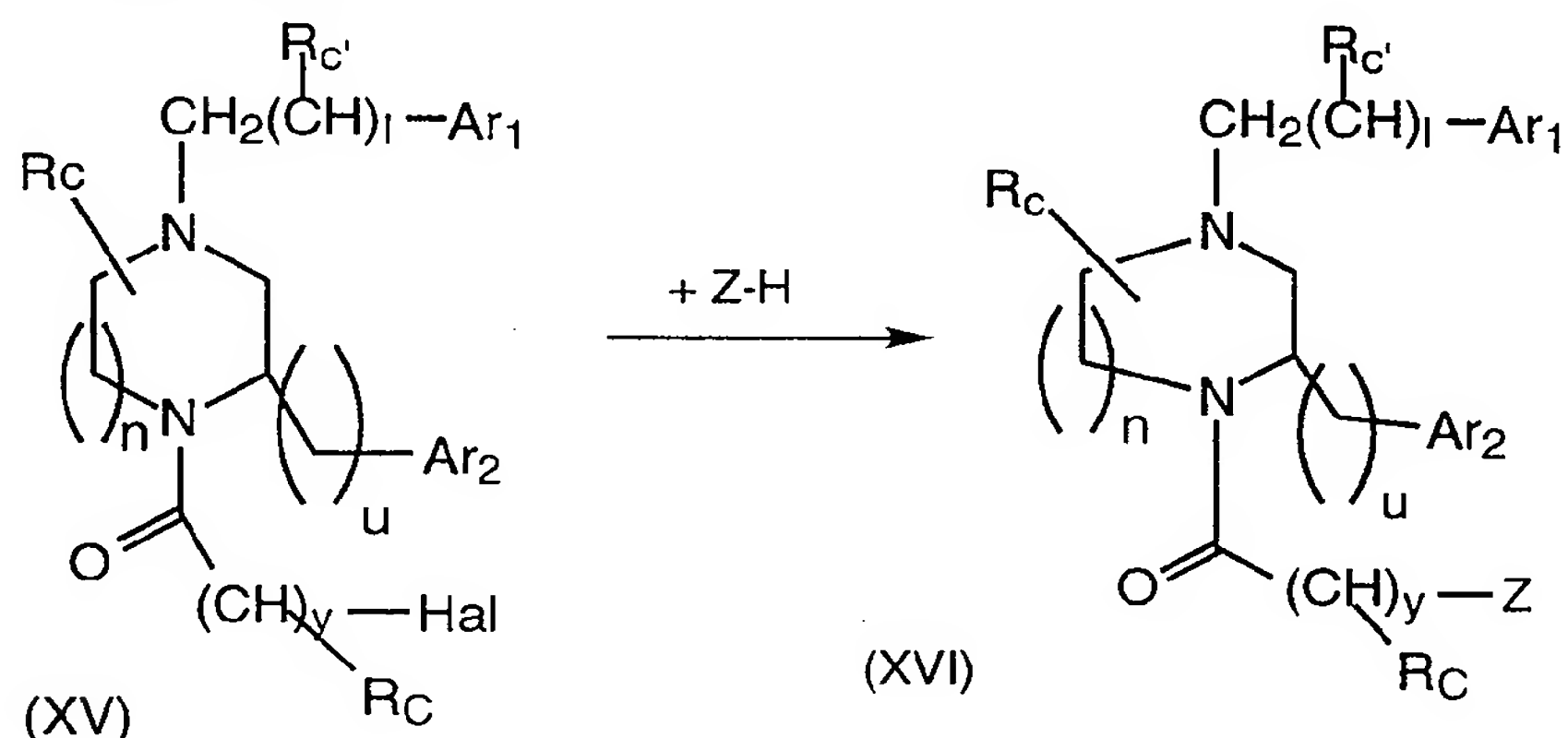
A compound of formula II may be converted to a compound of formula IV by the processes described in Method 1 above or Method 6 below.

- 5 **Method 4.** The intermediates of formula IV or IVA, formed via any of the previous methods, may be further processed as follows. A compound of formula IVA will be used in the Schemes. Reaction of a compound of formula IVA with an activated halo-acid, generally the acid halide of formula XIV, in which Hal represents Cl, Br, or I, yields the acylated derivative of formula XV that is, m is 1 for formula I. An organic base is used to take up the hydrogen halide formed in the reaction, suitable bases being triethylamine (TEA) and Hünig's Base. Suitable reaction media include halogenated solvents, such as methylene chloride and chloroform. The reaction is preferably run at low temperature, at least initially. Suitable temperatures are in the region of -50°C down to -80°C. Later in the reaction it may be desirable to allow the mixture to warm up to about RT to ensure completion of the reaction.

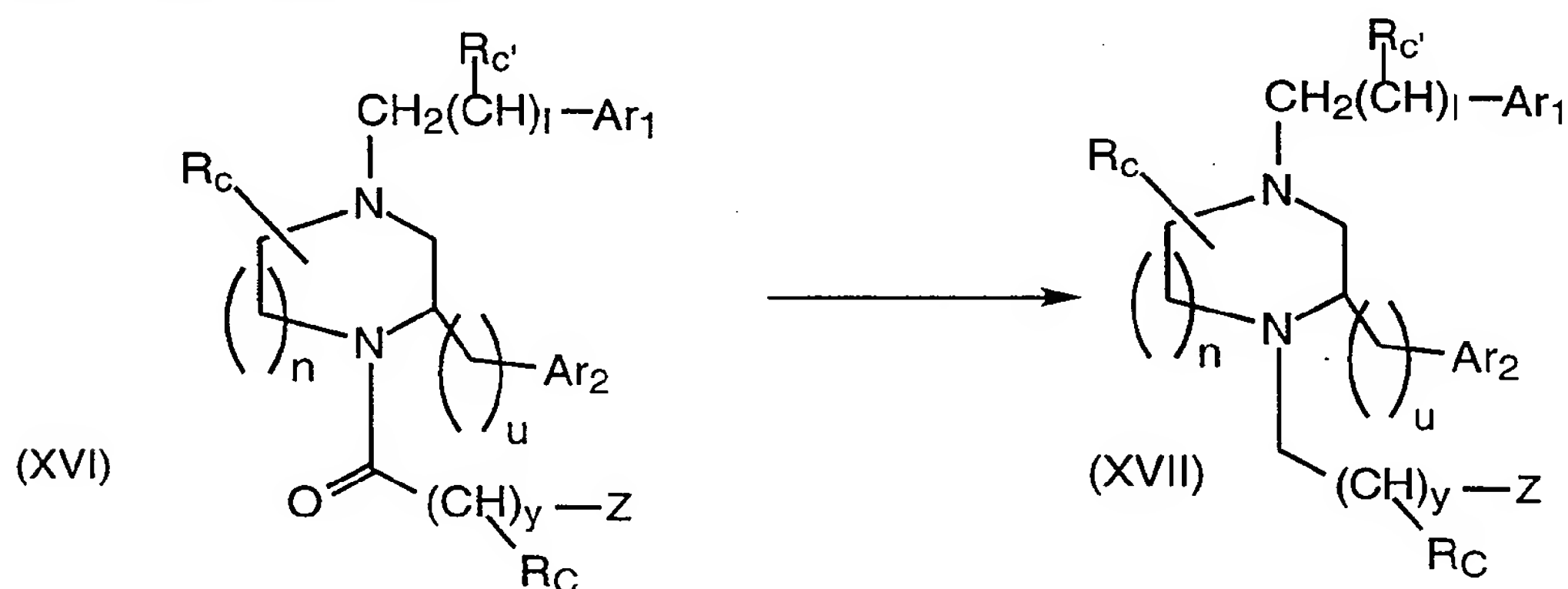


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Reaction of the halogenated amides of formula XV with an amine of formula Z-H results in formation of the products of formula XVI, which are compounds of the invention in which X is O and m is 1. Compounds of formula XVI have been modified to show the fact that these products could have been prepared from compounds of formula IVA as well as from IV. Suitable solvents for this reaction are halogenated hydrocarbons, such as methylene chloride, and an organic base is present to absorb the H-Hal formed. Appropriate bases include Hünig's Base. The reaction is performed at or around RT, a suitable temperature being generally in the range of from 0°C to 40°C. Reaction is complete within 1 to 48 hours.



Method 5. Compounds of formula XVI where $y \neq 0$ may be converted to other compounds of the invention of formula XVII by reduction under controlled conditions.

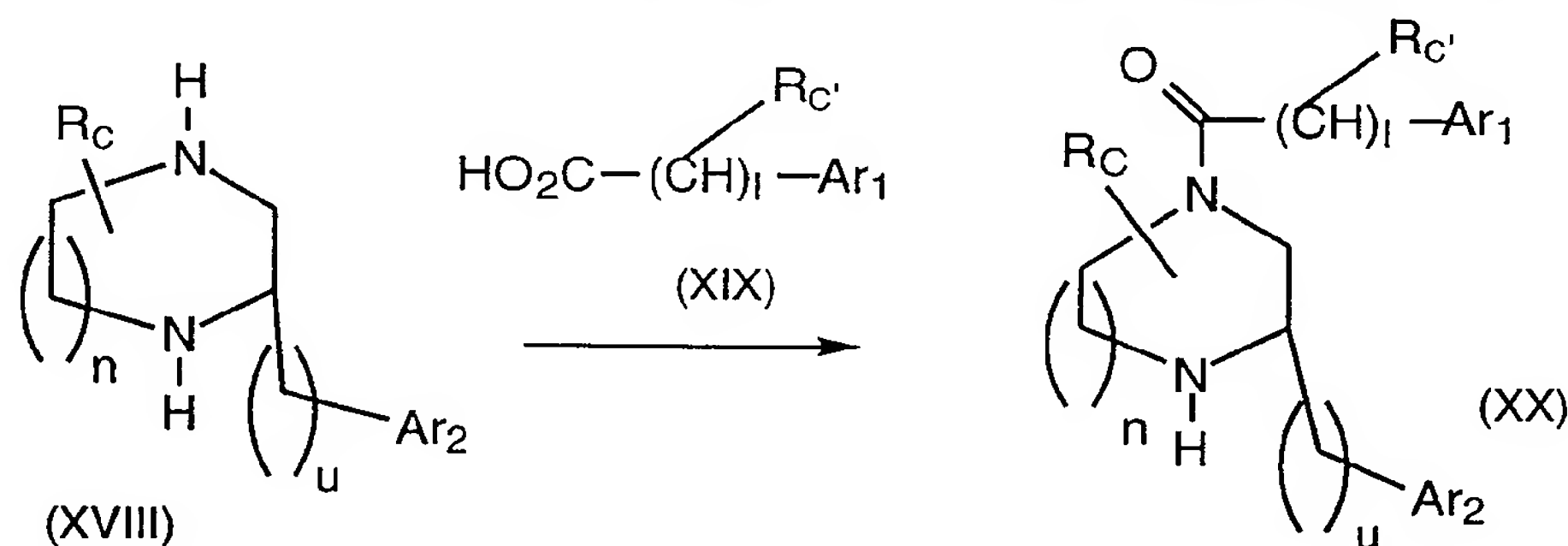


Suitable reducing agents to effect this transformation include the borane-dimethyl sulfide complex, as well as other less selective reagents, such as LAH, (assuming that no other group reactive to LAH is present), Red-Al®, and diborane in ether. Effective temperatures for the

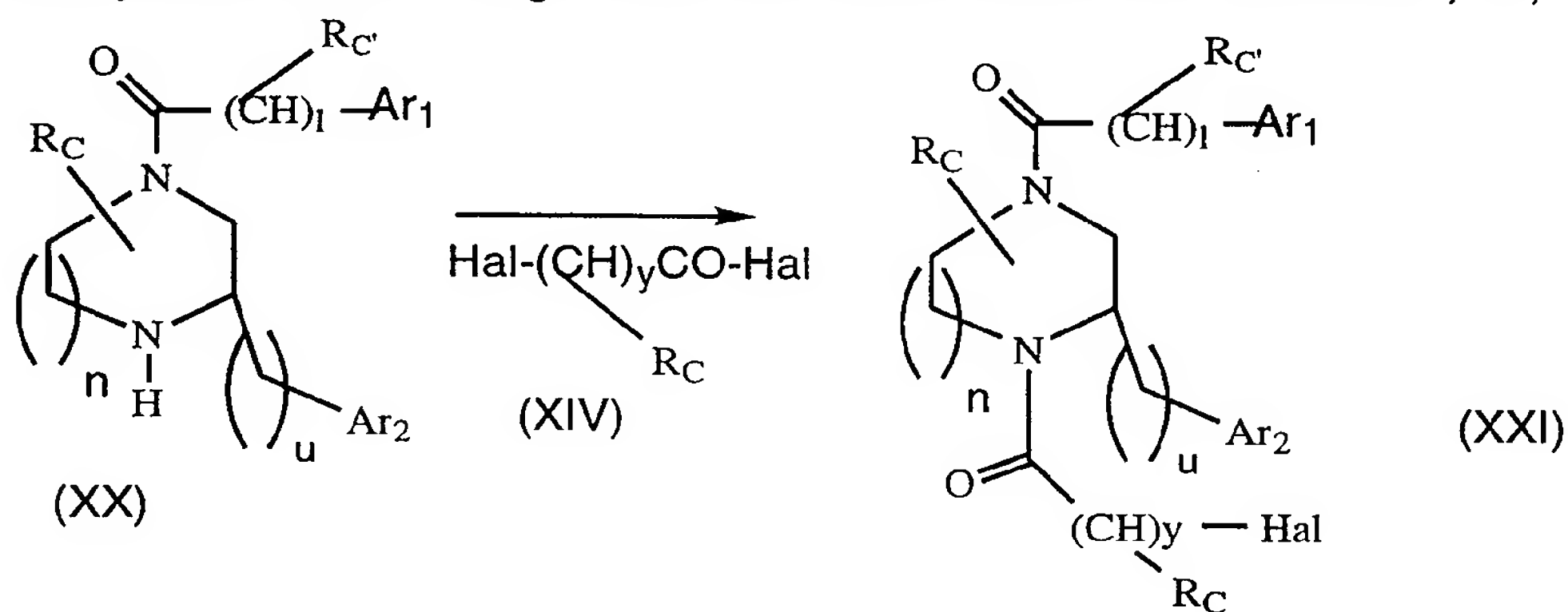
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borane-dimethylsulfide complex to reduce compounds of formula XVI, range from RT to the reflux temperature of the solution of the reagent in THF (about 80°C).

Method 6. Intermediates of the formula XVIII may be selectively acylated by coupling with an acid of the formula XIX. Standard coupling techniques may be applied, for example the use of HOBT, a water-soluble carbodiimide, such as DEC, and an organic base, such as Et₃N, in a non-hydroxylic solvent, such as CH₂Cl₂, at a temperature of about -20°C initially. The mixture may be allowed to warm to RT to complete the reaction. The product of reaction is the amide of formula XX.



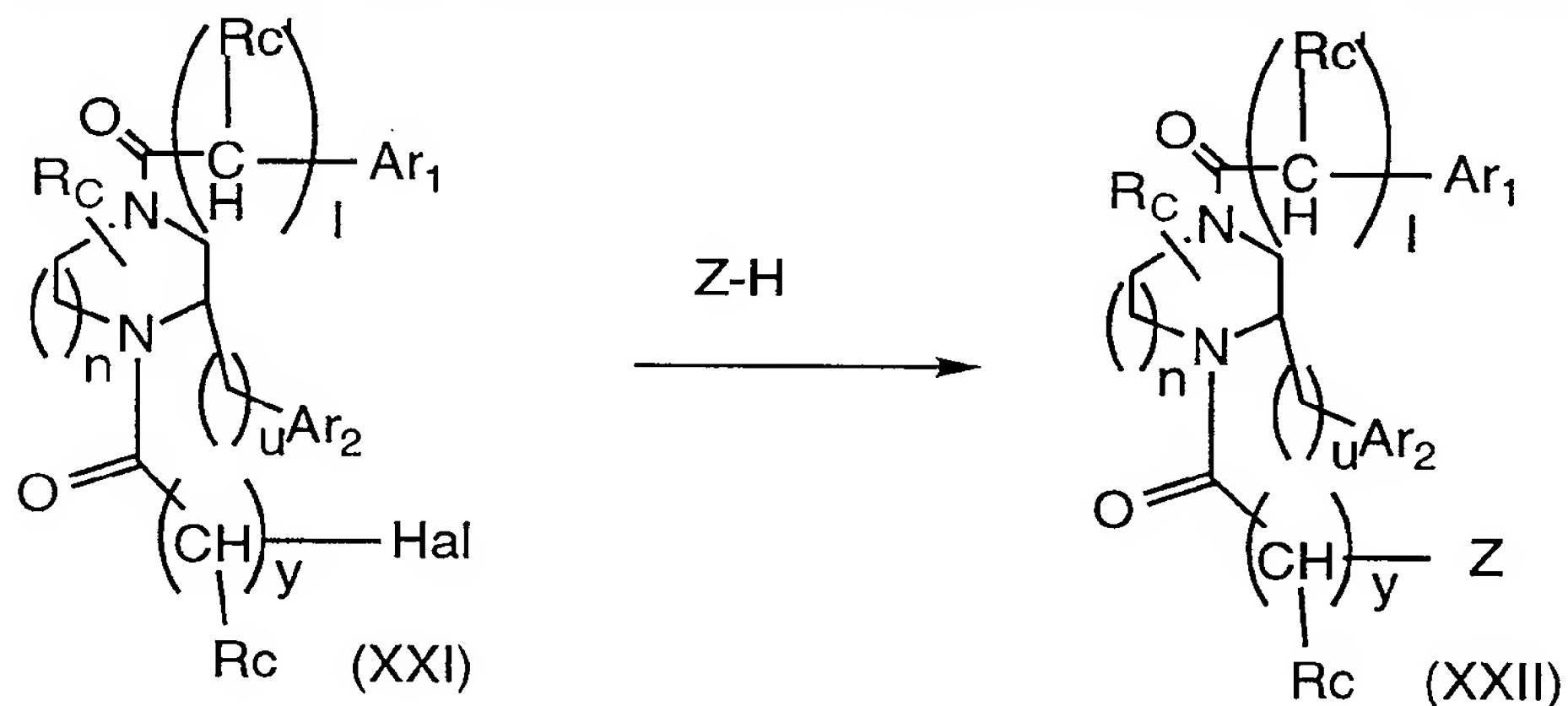
Compounds of the formula XX, may be further acylated using an acid halide of formula XIV. The reaction is run, preferably at about 0°C, over a period of 1 to 12 hours, in a halogenated solvent, such as methylene chloride or similar solvent. An organic tertiary amine is used to absorb the H-Hal produced in the reaction. Suitable amines include triethylamine and Hünig's Base. As used herein Hal means Cl, Br, or I.



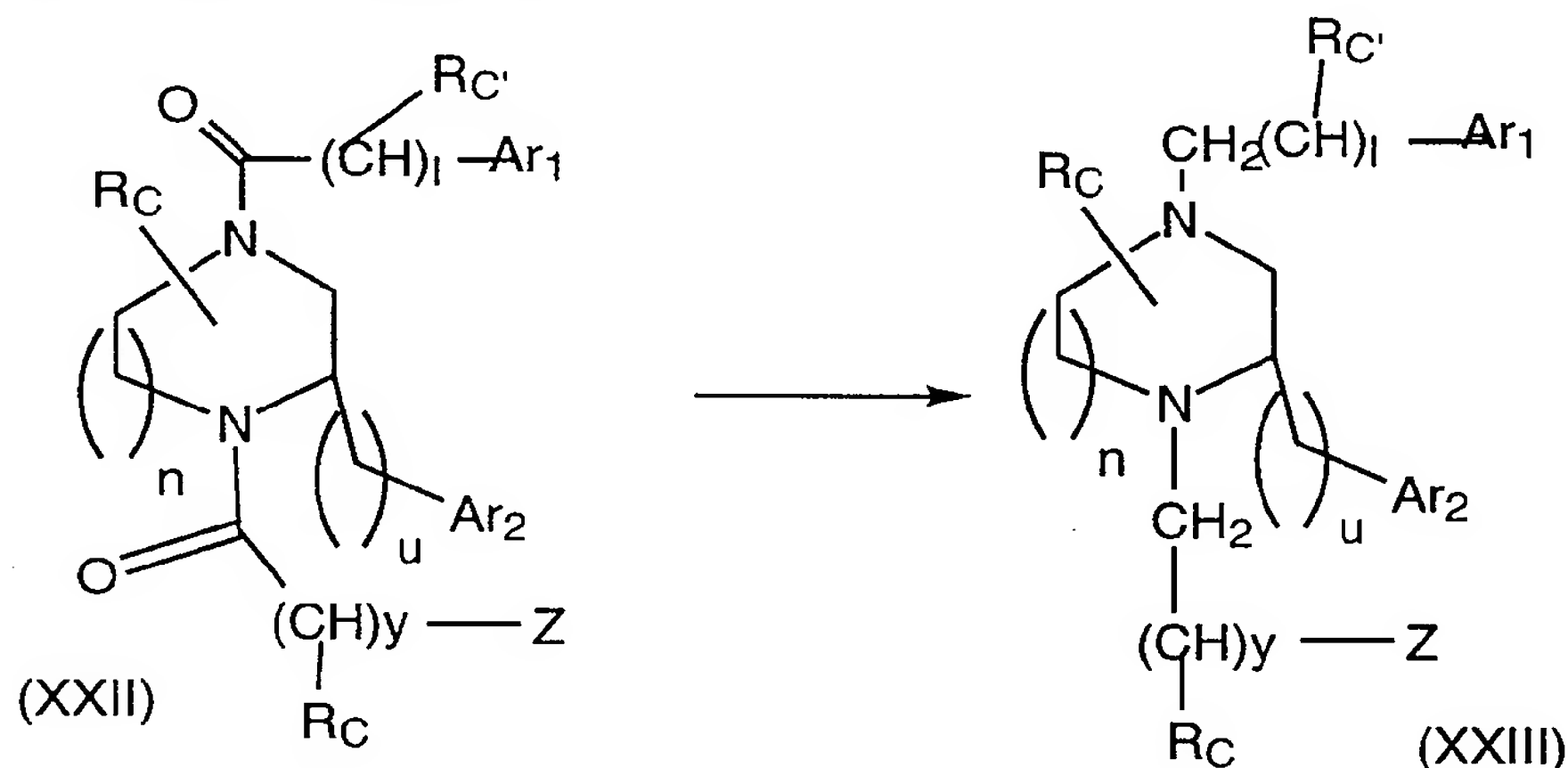
The compounds of formula XXI, that is, m is 1 in formula I, y = 1-3, l = 0-2 may be used for further reaction without isolation. Additional organic base, for instance, Hünig's Base, is added to the mixture followed by Z-H, at or around -78°C. The reaction is completed by

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allowing the mixture to warm to RT overnight yielding the compounds of formula XXII after work-up and purification by standard methods.



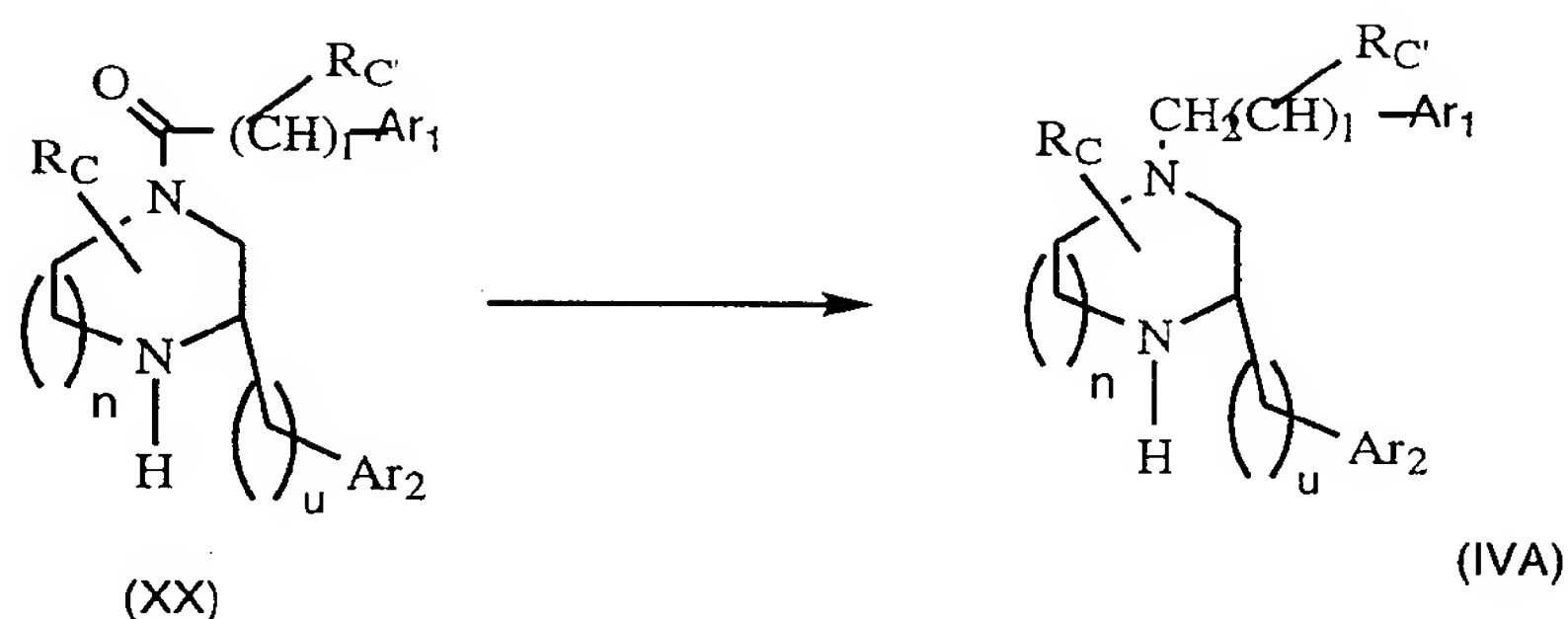
5 The compounds of formula XXII, in which $y = 1-3$ may be converted to other products of formula XXIII by reduction under controlled conditions.



10 Suitable reducing agents to effect this transformation include the borane-methyl sulfide complex, as well as other less selective reagents, such as LAH, Red-Al[®], and diborane in ether or other unreactive solvents, such as THF. Using the borane-methyl sulfide complex in THF, at the reflux temperature of the solution, which is about 80°C, the reaction is complete in about 2 hours to 48 hours depending on the precise substrate.

15 **Method 7.** The acylated derivatives of formula XX from Method 6 may be reduced to the saturated alkyl chain derivatives of formula IVA.

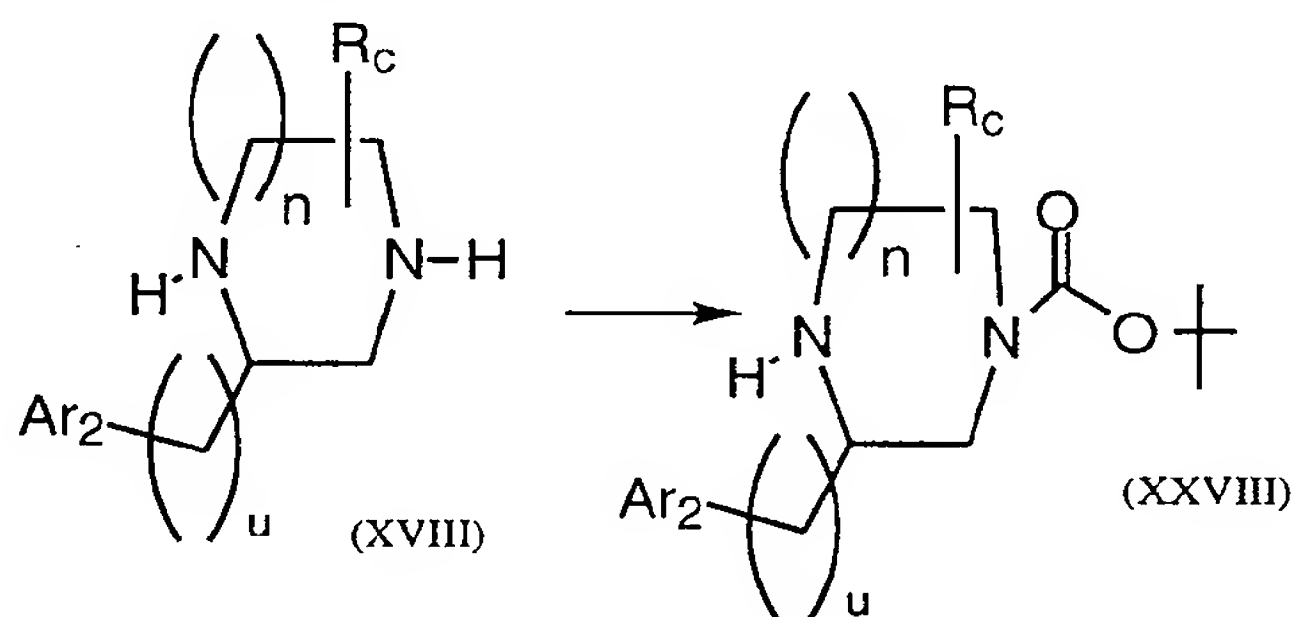
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The process to conduct this conversion is the same as described in Method 6 for conversion of a compound of formula XXII to a compound of formula XXIII. The reagent of preference is the borane-methyl sulfide complex.

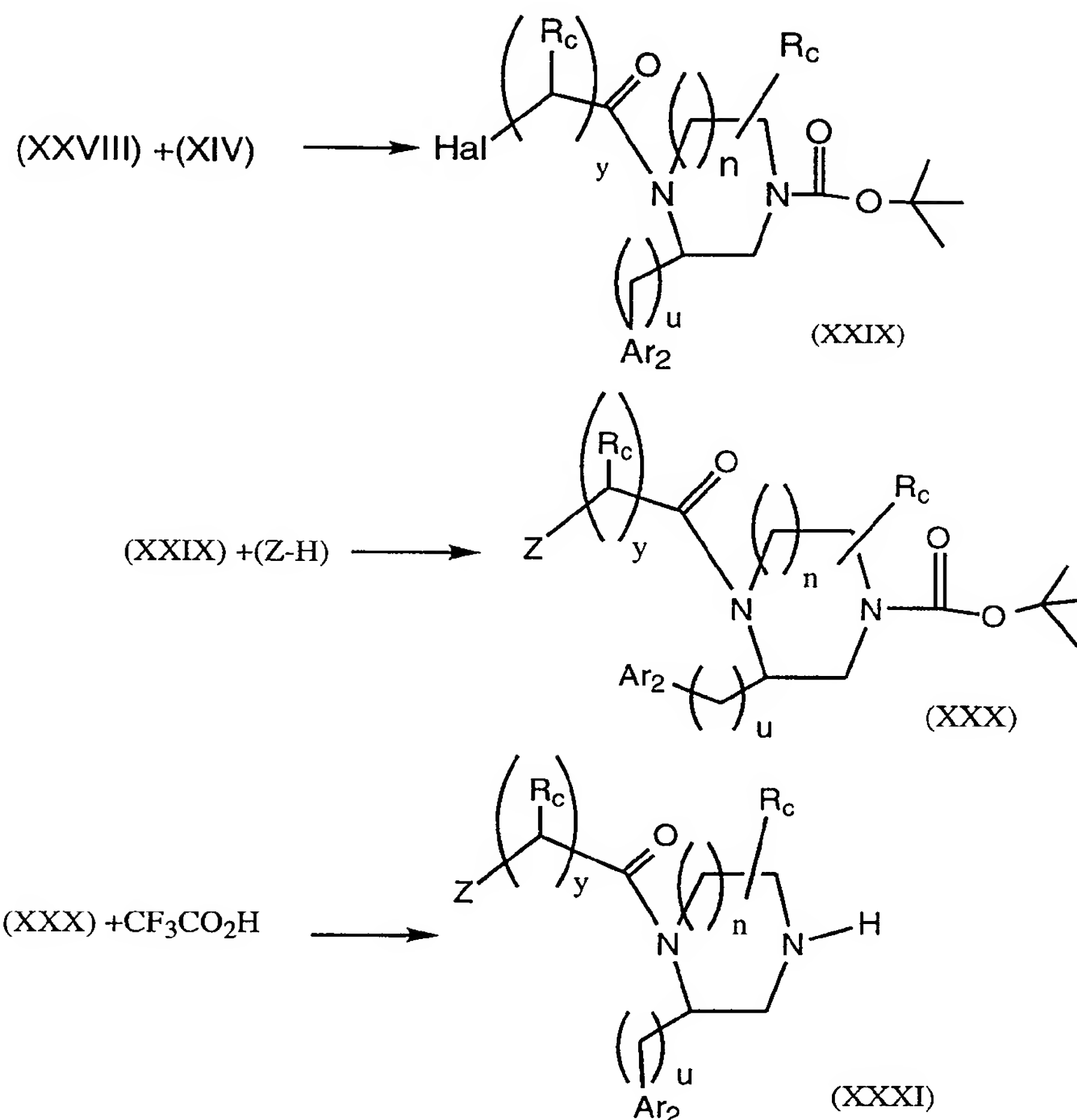
A compound of formula IVA can be converted to a target compound of formula XVI as described previously.

An alternate route to compounds of structure (XXII) also starts with compound (XVIII). Initial reaction with an amine protecting group reagent, preferably BOC anhydride, produces the N-t-butyloxycarbonyl derivative of the formula XXVIII.



As before, reaction occurs preferentially at the nitrogen atom further away from the Ar₂ group. Reaction of this intermediate with a reagent of structure (XIV) as described above, leads to the halo-derivative (XXIX). Reaction of (XXIX) with Z-H, again as described above, produces the intermediate (XXX) which may be de-protected to produce (XXXI). Suitable reagents include trifluoroacetic acid and HCl.

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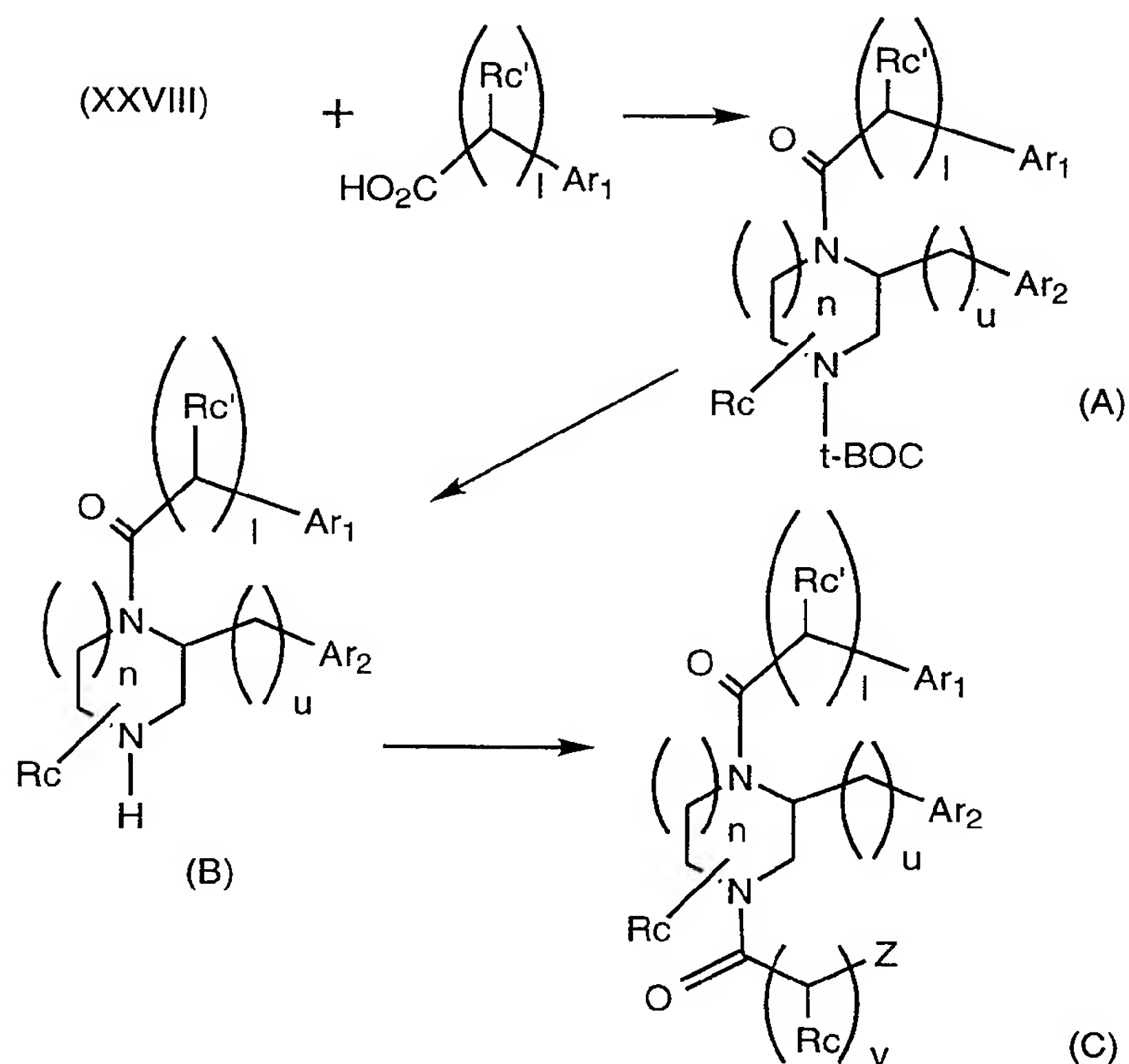


Reaction of (XXXI) with a carboxylic acid (XIX) under coupling
 5 conditions as described above, leads to the products of formula (XXII).
Method 7a. Synthesis of the compounds of the invention wherein the
 pendant aromatic group Ar_2 , or the pendant aromatic group Ar_2 and its
 sidechain, are located in the alternate ring position to the compounds of
 formula XXII (i.e. compounds of formula C below), may be prepared
 10 using compounds of formula XXVIII from method 7 as starting materials.
 Coupling of compounds of formula XXVIII with any of the acids

$Ar_1 - \overset{\overset{R_{c'}}{|}}{(CH)_l}CO_2H$ under standard coupling conditions, for instance using
 HOBT, Et_3N and DEC in CH_2Cl_2 , produces the intermediate (A).

Removal of the t-BOC or other protecting group under standard
 15 conditions releases the free amine (B). Acylation of (B) and further
 reaction with Z-H proceeds as described in Method 6 for the conversion
 of (XX) via (XXI) to (XXII) to produce compound (C) of the invention.

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The Z-H starting materials are commercially available or are prepared using methods known in the art.

Using procedures similar to those described in the above or using procedures known to those skilled in the art, one can produce all of the compounds of formula I of the invention. For example, one can obtain compounds of the invention of formula I wherein the R_C moiety is on various carbons of the piperazine ring.

The *in vitro* and *in vivo* activity of the compounds of formula I can be determined by various procedures known in the art, such as a test for their ability to inhibit the activity of the NK₁ agonist Substance P, an isolated hamster trachea NK₂ assay, a test of the effect of NK₁ antagonists on Substance P-induced airway microvascular leakage, measurement of NK₂ activity in vivo in guinea pigs, measurement of bronchoconstriction due to NKA, and neurokinin receptor binding assay(s). Typical procedures are published in previously cited WO96/34864.

For all of the compounds of the invention, the NK₁ binding is in a range of about 0-100 % inhibition at 1 μM concentration. For all of the

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compounds of the invention, the NK₂ binding is in a range of about 0-100 % inhibition at 1 μ M concentration. It should be understood that while the NK binding for certain compounds of the invention is as low as 0% at 1 μ M concentration, that at higher concentrations these
5 compounds are expected to have NK binding inhibition activity.

The K_i of a compound is that concentration at which the compound caused 50% inhibition of either NK₁ or NK₂. For those compounds of the invention having higher than 50% inhibition of NK₁, K_i's for NK₁ are determined.

10 For those compounds of the invention having higher than 50% inhibition of NK₂, K_i's for NK₂ are determined.

Compounds of formula I exhibit NK₁ and NK₂ antagonist activity to varying degrees, i.e., certain compounds have strong NK₁ antagonist activity, but weaker NK₂ antagonist activity. Others are strong NK₂
15 antagonists, but weaker NK₁ antagonists. Certain compounds have both strong NK₁ and NK₂ antagonist activities. Some compounds can also be NK₃ antagonists.

Many compounds of formula I have an asymmetric center and therefore exist as a pair of enantiomers. In such cases, one enantiomer
20 can have different biological activity than the other. For example, one enantiomer can have strong NK₁ activity and weak NK₂ activity while the other enantiomer has weak NK₁ activity and strong NK₂ activity.

Certain compounds of formula I have been found to be antagonists of both NK₁ and NK₂ receptors, and are therefore useful in
25 treating conditions caused or aggravated by the activity of NK₁ and NK₂ receptors.

The present invention also relates to a pharmaceutical composition comprising a compound of formula I and a pharmaceutically acceptable carrier. Compounds of this invention can
30 be administered in conventional oral dosage forms such as capsules, tablets, powders, cachets, suspensions or solutions, or in injectable dosage forms such as solutions, suspensions, or powders for reconstitution. The pharmaceutical compositions can be prepared with conventional excipients and additives, using well known formulation
35 techniques. Pharmaceutically acceptable excipients and additives include nontoxic and chemically compatible fillers, binders,

disintegrants, buffers, preservatives, anti-oxidants, lubricants, flavorings, thickeners, coloring agents, emulsifiers and the like.

The daily dose of a compound of formula I for treating asthma, cough, bronchospasm, inflammatory disease, migraine, nociception and gastrointestinal disorders is about 0.1 mg to about 20 mg/kg of body weight per day, preferably about 0.5 to about 15 mg/kg, more preferably 0.5 to about 5 mg/kg. For an average body weight of 70 kg, the dosage range is therefore from about 1 to about 1500 mg of drug per day, preferably about 50 to about 100 mg, given in a single dose or 2-4 divided doses. The exact dose, however is determined by the attending clinician, and is dependent on the potency of the compound administered, the age, weight, condition and response of the patient.

The invention disclosed herein is exemplified by the following examples, which should not be construed to limit the scope of the disclosure. Alternative mechanistic pathways and analogous structures within the scope of the invention will be apparent to those skilled in the art.

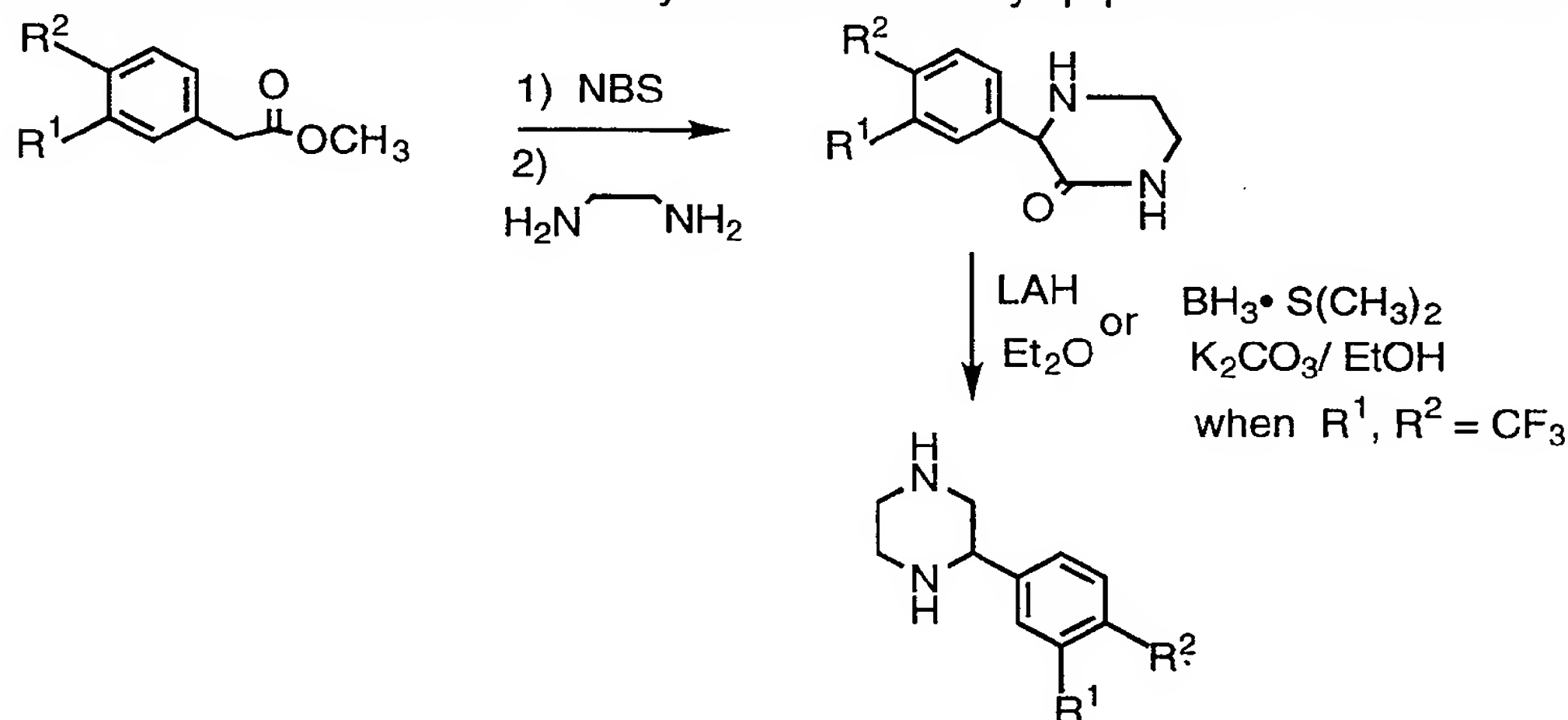
PREPARATIVE EXAMPLE 1

2-(3,4-dichlorophenyl)piperazine

20 A. Synthesis of racemic compound

2-(3,4-Dichlorophenyl)piperazine was synthesized according to the method published in J. Med.Chem. 9,191,1966.

A. General method for the synthesis of 2-aryl-piperazine derivatives.



R^1 = Cl, H or other substituents i.e. OCH_3 , CF_3 , Br, I, F, etc.

R^2 = Cl, H or other substituents i.e. OCH_3 , CF_3 , Br, I, F, etc.

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B. Resolution of 2-(3,4-dichlorophenyl)piperazine

Step 1: A solution of 2-(3,4-dichlorophenyl)piperazine (36.05 g, 0.156 mol) in CH₃OH (200 mL) was treated with a solution containing two equivalents of N-acetyl-L-leucine (54.02 g, 0.312 mol) and heated until
5 all of the material was dissolved. EtOAc (2.2 L) was added to this solution and allowed to stand at ambient temperature overnight. The solvent phase was decanted from the precipitated salt and concentrated in vacuo. This procedure was repeated using 37.88 g of 2-(3,4-dichloro-
phenyl)piperazine (0.164 mol) and 56.68 g of N-acetyl-L-leucine (0.327
10 mol).

Step 2: The concentrated salts from both solvent phases in step 1 were combined and heated in methanol (550 mL) until all of the material dissolved. EtOAc (2.75 L) was added to this solution and allowed to stand at ambient temperature overnight. The solvent phase was
15 decanted from the precipitated salt and concentrated in vacuo to give ~95 g of piperazine salt (72% ee of enantiomer A).

Step 3: The salt from the solvent phase in step 2 was dissolved in a solution of H₂O (800 mL) and aq. ammonia (400 mL) and extracted with CH₂Cl₂ (4 x 400 mL). The combined organic layers were dried with
20 MgSO₄ and concentrated to give 37 g of the piperazine free base. The free base was recrystallized three times from hexane (890, 600 and 450 mL) to give 16 g of piperazine (>99.9% ee of enantiomer A).

$$[\alpha]_{\text{D}}^{24.7^{\circ}\text{C}} = -45.0^{\circ}(\text{MeOH})$$

Step 4: The precipitated salts from step 1 were combined and heated in methanol (220 mL) until all of the material dissolved. EtOAc (2.2 L) was
25 added to this solution and allowed to stand at ambient temperature overnight. The solvent phase was decanted from the precipitated salt and dried in vacuo to give ~43 g of piperazine salt (93% ee of enantiomer B).

Step 5: A 12.3 g portion of salt (75% ee of enantiomer B) prepared by an analogous procedure to that in step 4 was dissolved in 0.5 M NaOH (400 mL) and extracted with CH₂Cl₂ (4 x 155 mL). The combined organic layers were dried with MgSO₄ and concentrated to give 3.72 g
30 of the piperazine free base. The free base was recrystallized twice from

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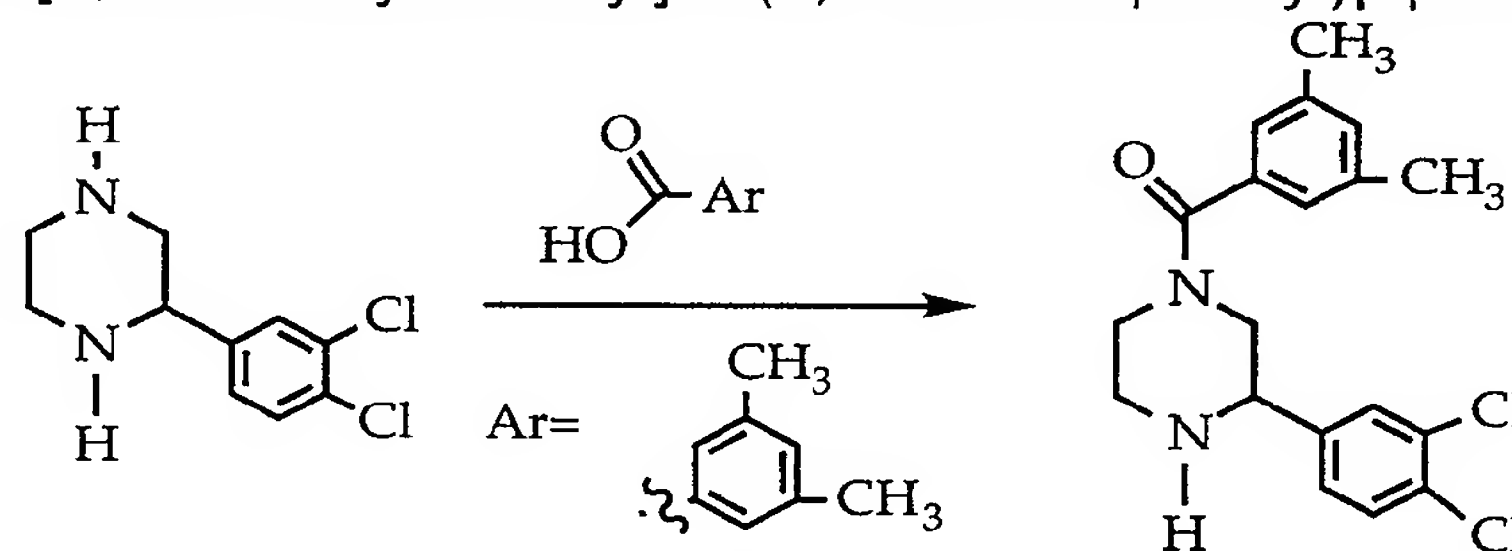
hexane (90 and 70 mL) to give 2.1 g of piperazine (98% ee of enantiomer B).

C. Analytical procedure for measuring piperazine enantiomeric purity.

The enantiomeric purity of the piperazine was measured by chiral HPLC analysis of the di-tert-butoxycarbonyl piperazine derivative. The di-tert-butoxycarbonyl derivative was prepared by adding a small piperazine sample (free base or salt) (~ .2 mg) to di-tert-butyl dicarbonate (~ 1 mg) and methanol (0.5 mL) and heating at 80°C for 1 h. If the piperazine sample is a salt, triethylamine (20 µL) is also added. The derivative was analyzed by HPLC using a ChiralPak AD column eluting with 95:5 hexane-isopropyl alcohol.

PREPARATIVE EXAMPLE 2

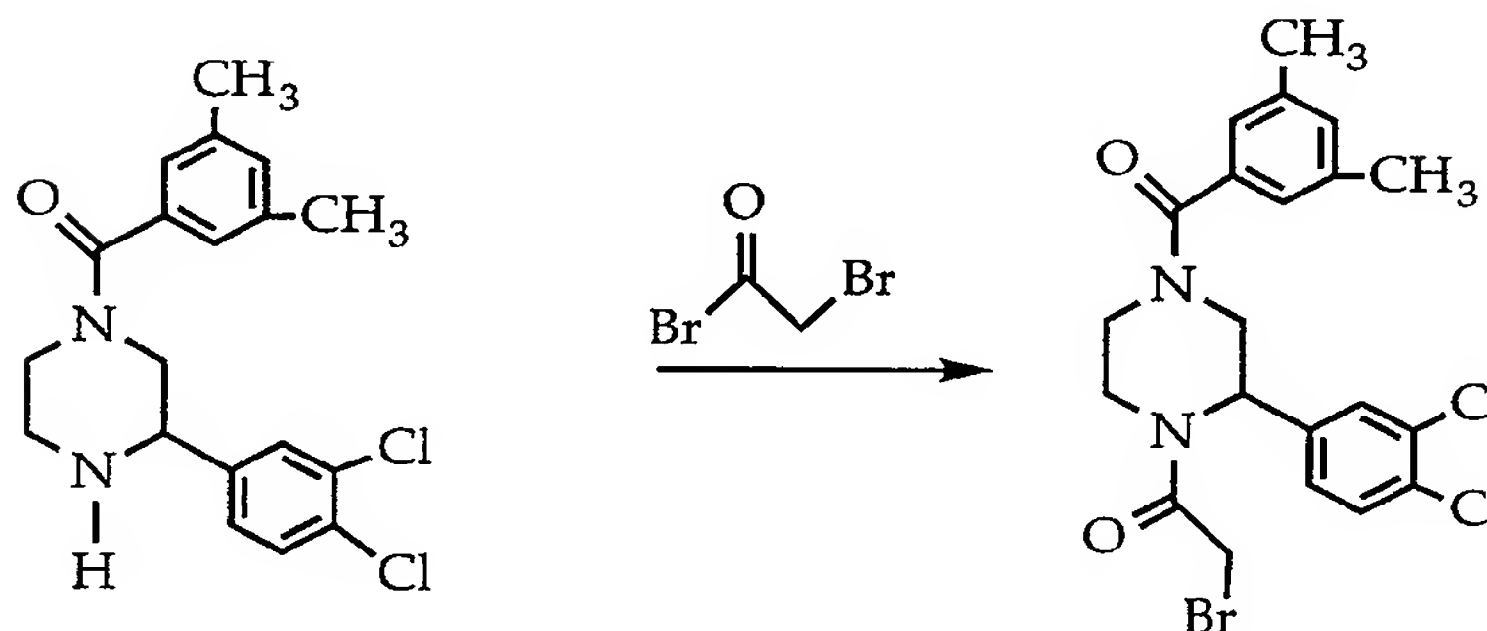
(+,-)-[3,5-dimethylbenzoyl]-3-(3,4-dichlorophenyl)piperazine



To a cooled solution of CH₂Cl₂ (600 mL) containing 2-(3,4-dichlorophenyl)piperazine (6.934 g, 30 mmol), 3,5-dimethylbenzoic acid (4.55 g, 30 mmol), and N-hydroxybenzotriazole monohydrate (4.05 g, 30 mmol) at -20 °C were added Et₃N (4.2 mL, 30 mmol) and N,N-dimethylaminopropylethylcarbodiimide (DEC) (5.86 g, 30 mmol) under nitrogen. The reaction was kept at -20 °C for an hour and gradually warmed to RT overnight. After stirring 22 hours, the reaction was complete and CH₂Cl₂ (200 mL) was added. The organic solution was washed with brine (150 mL, 3x), dried over MgSO₄, filtered and concentrated under vacuum to give 8.2 g of crude product. The product was crystallized from CH₂Cl₂/Hexane to give a light yellow solid (6.3 g, 17.34 mmol, 57.8%). M.p.139-141°C; FAB MS [M+1]⁺ ³⁵Cl 363.1.

PREPARATIVE EXAMPLE 3

(+,-)-bromoacetyl-2-(3,4-dichlorophenyl)-4-(3,5-dimethylbenzoyl)piperazine

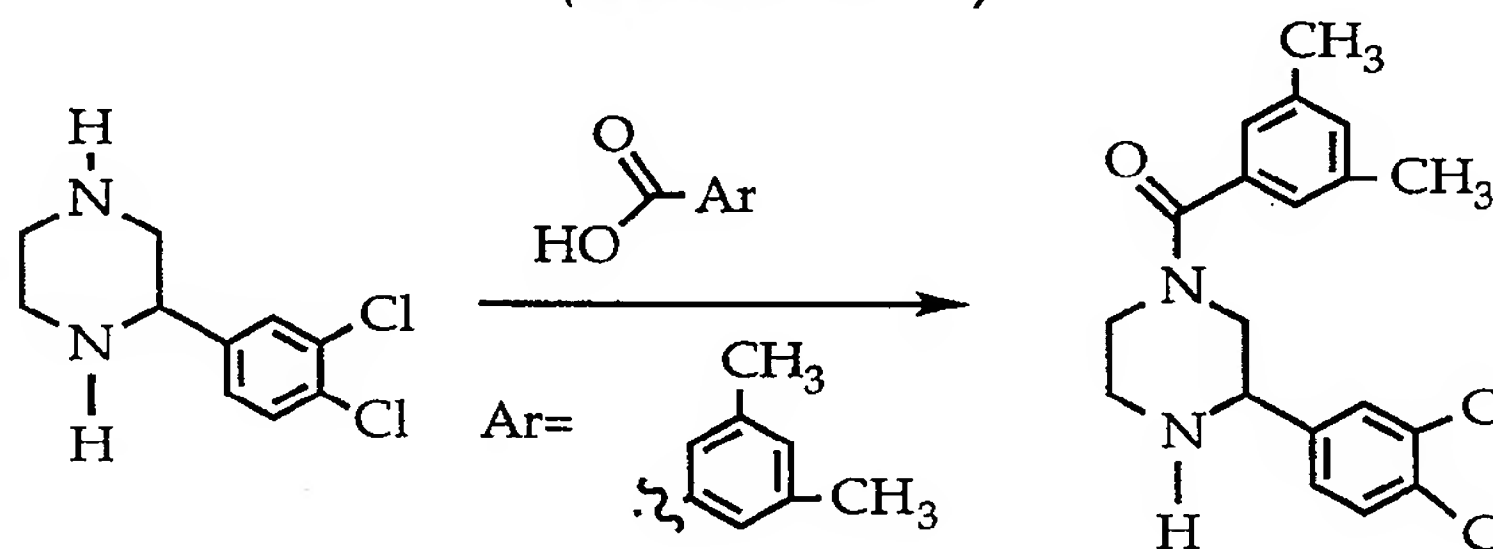


5 To a cooled solution of (+,-)-[3,5-dimethylbenzoyl]-3-(3,4-dichlorophenyl)piperazine (11.5 g, 31.65 mmol) in CH₂Cl₂ (200 mL) at 0 °C was added Hünig's base (4.5 g, 35 mmol) and bromoacetyl bromide (6.4 g, 31.65 mmol). The solution was stirred at 0 °C overnight under N₂. After completion the reaction was diluted with CH₂Cl₂ (400 mL) and washed with brine (300 mL, 2x), dried over MgSO₄, filtered and concentrated. The crude material was purified by flash grade silica gel chromatography, eluting with 2% [NH₄OH/MeOH (1:9)] / 98% CH₂Cl₂ to give the title compound as a light yellow solid (7.1 g, 47.3%), m.p. 77-79 °C, FAB MS [M+1]⁺ ³⁵Cl, ⁷⁹Br 482.9, 484.9.

15

PREPARATIVE EXAMPLE 4

(+)-[3,5-dimethylbenzoyl]-3-(3,4-dichlorophenyl)piperazine
(Enantiomer B)



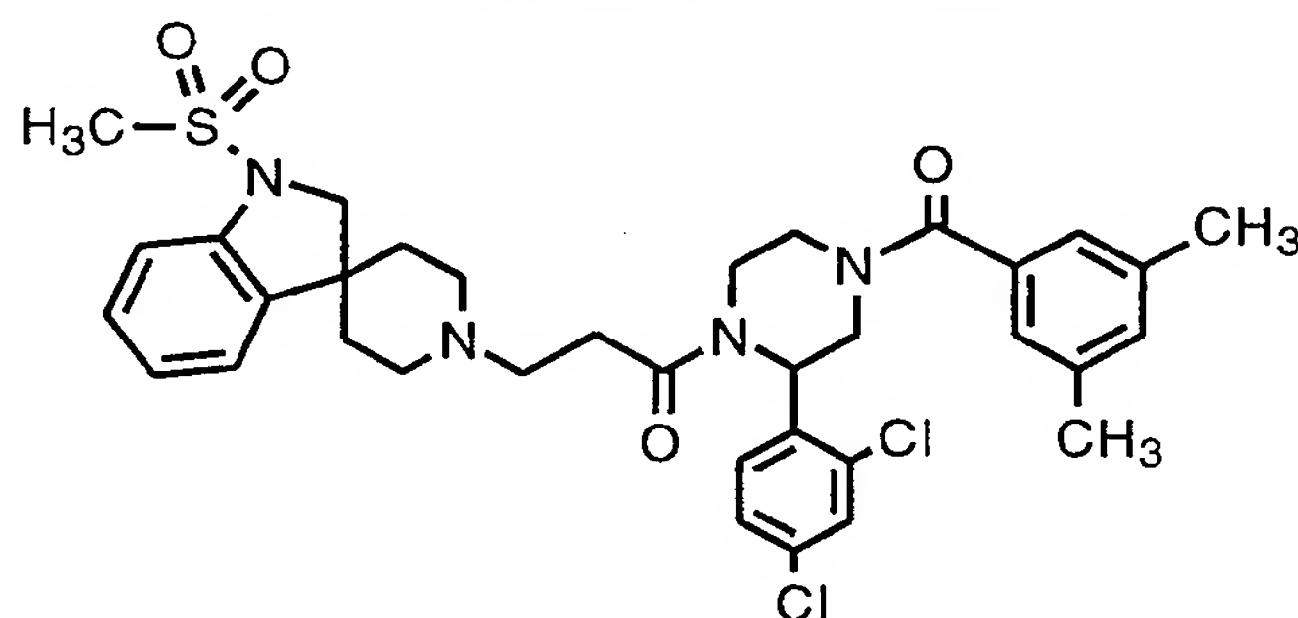
20 The title compound was prepared by an analogous method to that described in Example 2 using (-)-2-(3,4-dichlorophenyl)piperazine in place of (+,-)-2-(3,4-dichlorophenyl)piperazine, m.p. 97-100 °C; FAB MS

[M+1]⁺ ³⁵Cl 363.1; $[\alpha]_D^{22.5^\circ} = +87.2^\circ$ (MeOH).

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EXAMPLE 1

2-(3,4-Dichlorophenyl)-4-(3,5-dimethylbenzoyl)-1-[1,2-dihydro-1-(methanesulfonyl)spiro[3H-indole-3,4'-piperidine]-1'-yl]-1-oxopropyl]-piperazine (Enantiomer B)



5

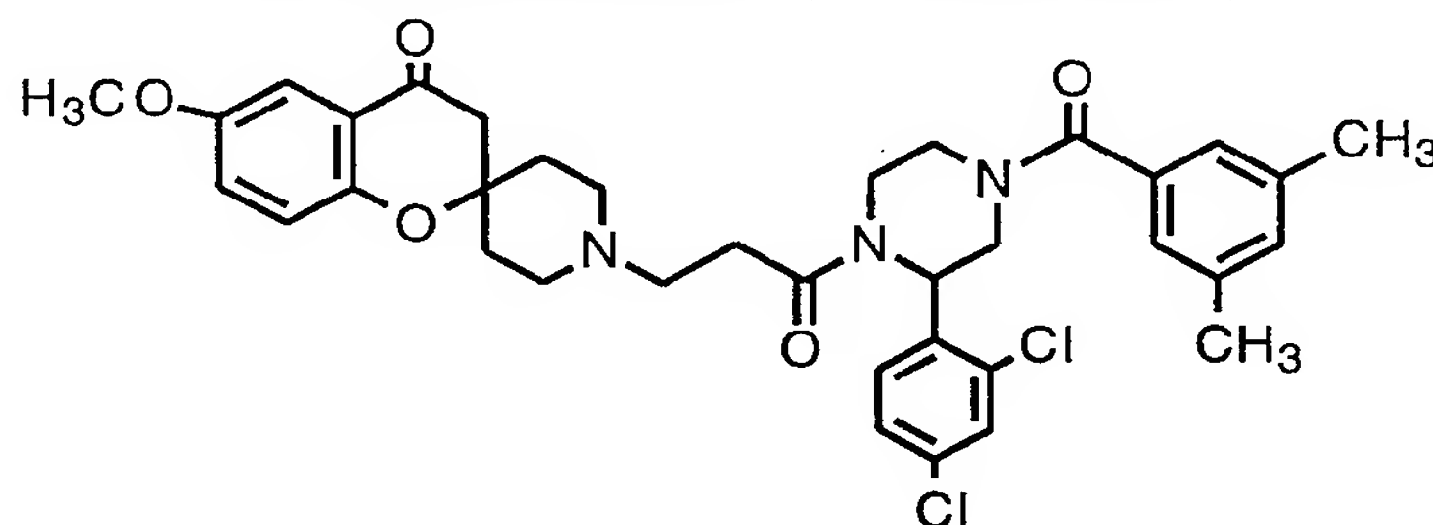
A cooled CH_2Cl_2 (3 mL) solution of the product of Preparative Example 4 (146 mg, 0.40 mmol) and Hünig's base (0.11 mL, 0.80 mmol) at -78°C was treated with 3-chloropropionyl chloride (0.038 mL, 0.40 mmol) and warmed to room temperature for 1 h. 1-Methanesulfonyl-spiro(indoline-3,4'-piperidine) (82 mg, 0.30 mmol) (prepared according to the procedure in Ong et al, *J. Med. Chem.*, 26, (1983), p. 981-986) was added to the reaction mixture and the resultant mixture was stirred for 48 h at room temperature. The reaction mixture was concentrated and purified by silica gel chromatography, eluting with 25:1:0.1 $\text{CH}_2\text{Cl}_2:\text{CH}_3\text{OH}:\text{conc. aq. NH}_3$ to give 39 mg of the title compound as a white solid. HRMS (FAB, $\text{M}+\text{H}^+$): m/e calc'd $[\text{C}_{35}\text{H}_{41}\text{Cl}_2\text{N}_4\text{O}_4\text{S}]^+$: 683.2226, found 683.2214.

10

15

EXAMPLE 2

2-(3,4-Dichlorophenyl)-1-[3-[3,4-dihydro-4-oxo-6-methoxy-spiro[2H-1-benzopyran-2,4'-piperidin]-1'-yl]-1-oxopropyl]-4-(3,5-dimethylbenzoyl)piperazine (Enantiomer B)



Using a method similar to that described in Example 1, substituting 6-methoxy-spiro[2H-1-benzopyran-2,4-piperidine] (prepared

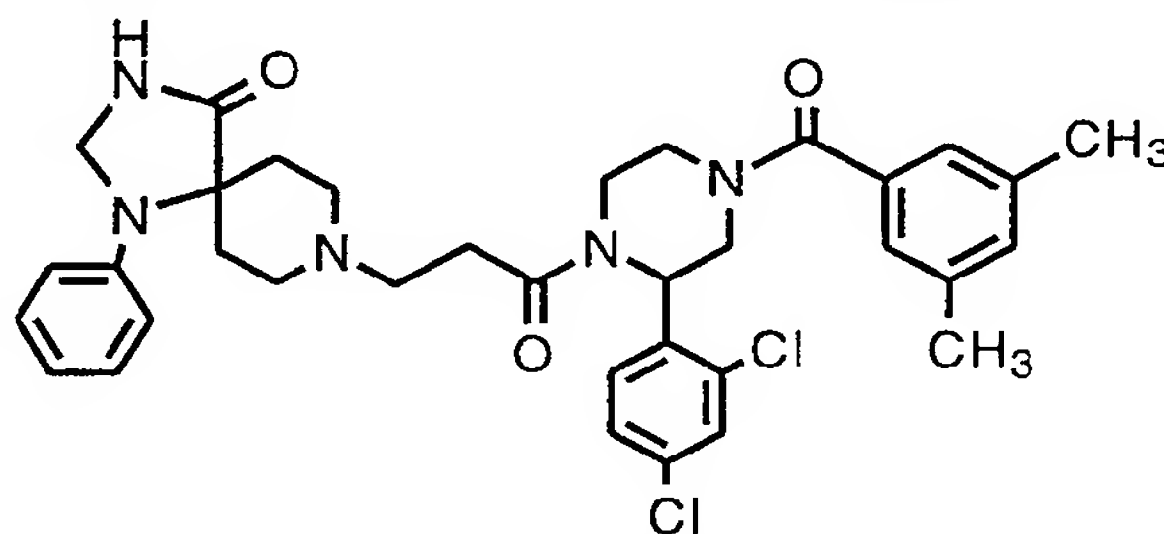
25

according to the procedure described in Yamato et al, *Chem. Pharm. Bull.*, 29 (1981), p. 3494-3498) for the spiro compound, the title compound was prepared. HRMS (FAB, M+H⁺): m/e calc'd [C₃₆H₄₀Cl₂N₃O₅]⁺: 664.2345, found 664.2365.

5

EXAMPLE 3

2-(3,4-Dichlorophenyl)-4-(3,5-dimethylbenzoyl)-1-[3-1-phenyl-4-oxo-1,3,8-triazaspiro[4.5]decan-8-yl)-1-oxopropyl]piperazine (Enantiomer B)

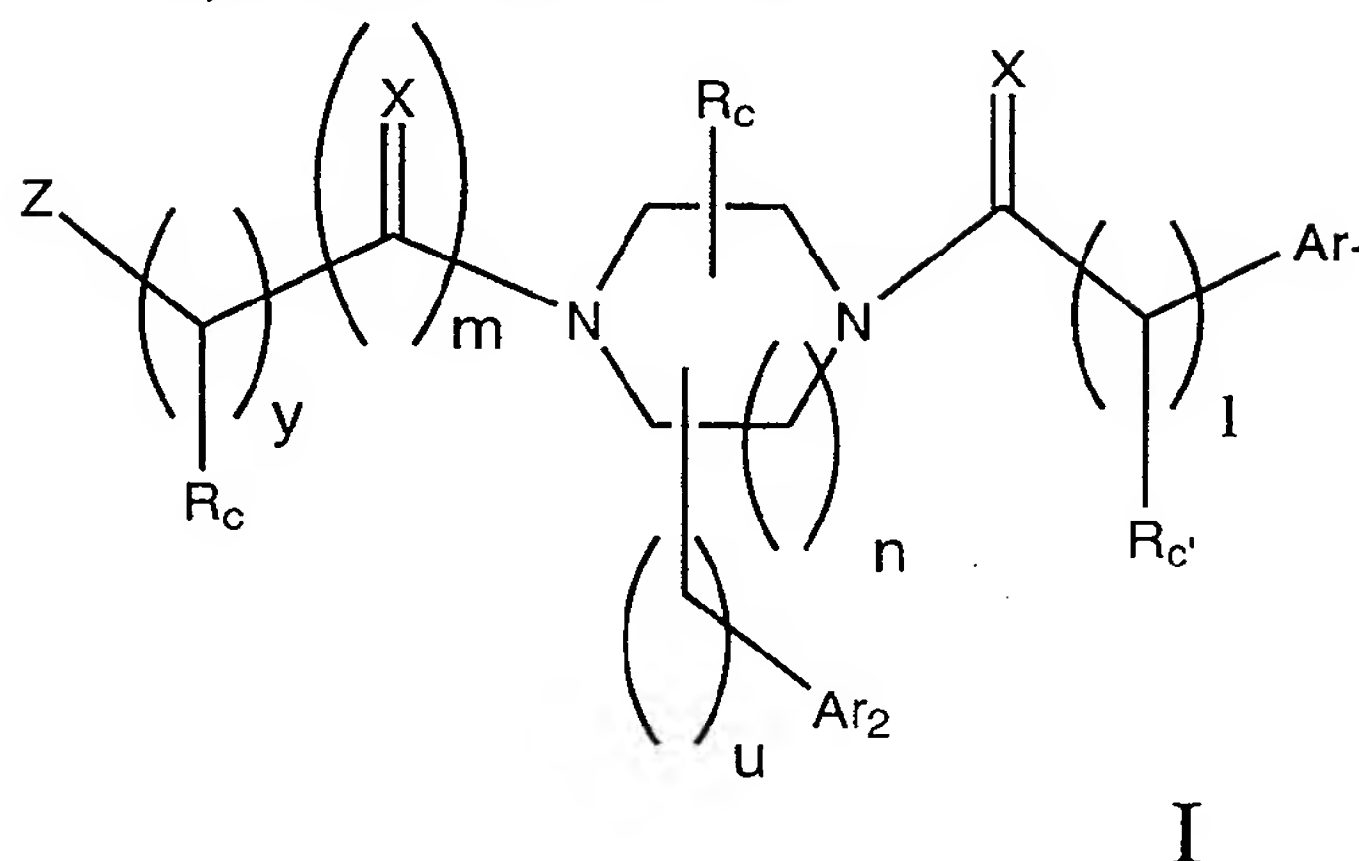


Using a method similar to that described in Example 1,
10 substituting 1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one for the spiro
compound, the title compound was prepared. HRMS (FAB, M+H⁺): m/e
calc'd [C₃₅H₄₀Cl₂N₅O₃]⁺: 648.2508, found 648.2509.

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WHAT IS CLAIMED IS:

1. A compound of the formula:



- 5 wherein

each X is independently selected from the group consisting of =O, (H,H), =NR_d, and =S;

n is 0 to 2; u is 0 to 2; l is 0 to 2;

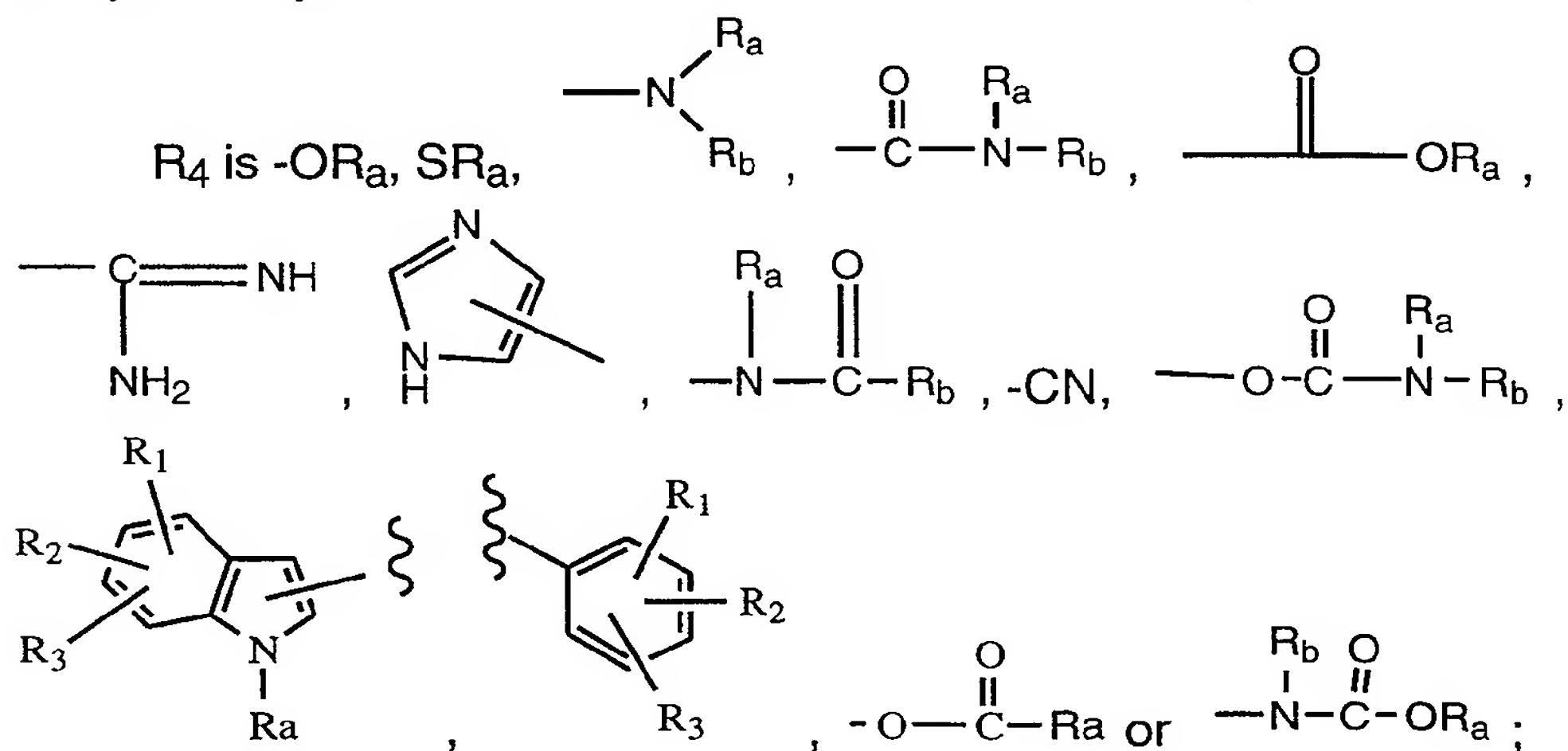
m is 1, and y is 1 to 3; or m is 2, and y is 0;

- 10 each R_c is independently selected from the group consisting of H, C₁-C₆ alkyl and -(CH₂)_{n1}-R₄, wherein n₁ is 1 to 6, with the proviso that



no more than one R_c is other than H in the R_c moiety;

R_d is independently selected from the group consisting of H, C₁-C₆ alkyl, -CN, -OR_a, phenyl, substituted phenyl, benzyl, substituted benzyl, or allyl;



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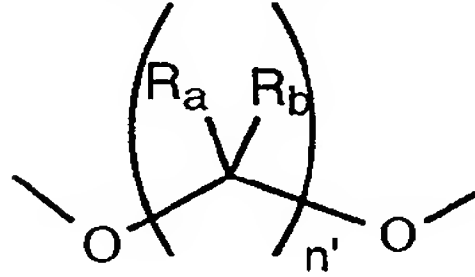
$R_{C'}$ is H, C_1 - C_6 alkyl or $(CH_2)_nOR_a$, with the proviso that no more than one $R_{C'}$ is other than H;

each R_a and R_b is independently selected from the group consisting of H, C_1 - C_6 alkyl, phenyl, substituted phenyl, benzyl, substituted benzyl and allyl; with the proviso that when R_4 is

5 $\begin{array}{c} R_b \quad O \\ | \quad || \\ -N-C-OR_a \end{array}$, R_a is not H; or when R_a and R_b are attached to the same nitrogen, then R_a and R_b , together with the nitrogen to which they are attached, can form a 4 to 7 member ring;

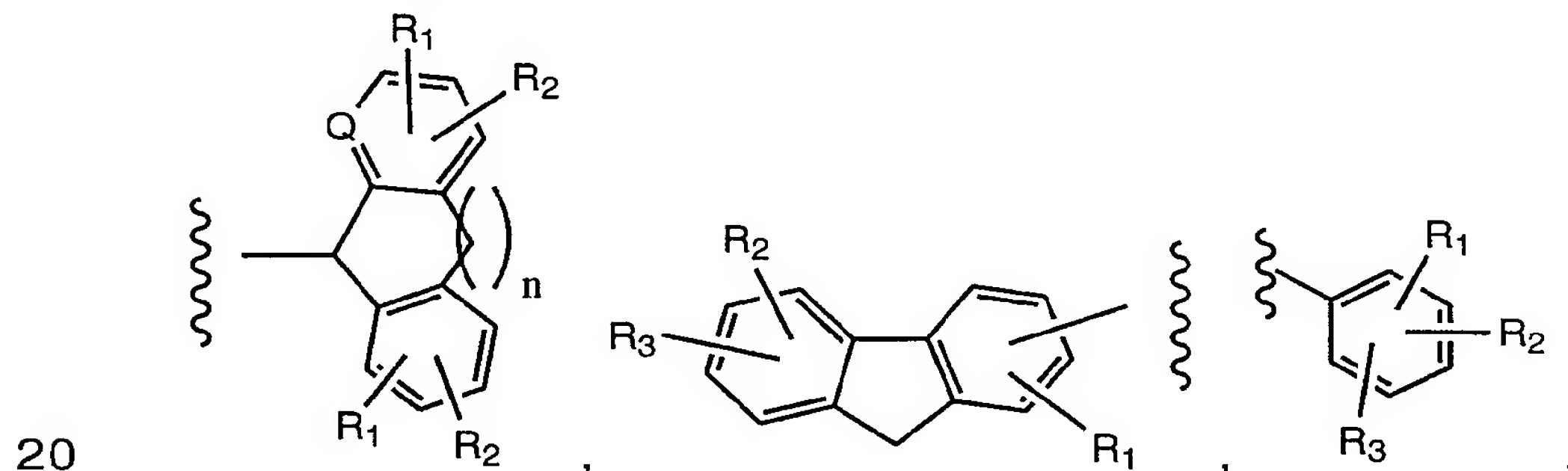
each R_1 and R_2 is independently selected from the group consisting of H, C_1 - C_6 alkyl, $-CF_3$, $-C_2F_5$, Cl, Br, I, F, $-NO_2$, $-OR_a$, $-CN$,

10 $-NR_aR_b$, $\begin{array}{c} O \\ || \\ -C-Ra \end{array}$, $-O-\begin{array}{c} O \\ || \\ -C-Ra \end{array}$, $\begin{array}{c} O \quad Ra \\ || \quad | \\ -O-C-N-Rb \end{array}$, $\begin{array}{c} R_b \quad O \\ | \quad || \\ -N-C-OR_a \end{array}$, $\begin{array}{c} Ra \quad O \\ | \quad || \\ -N-C-Rb \end{array}$, $\begin{array}{c} O \\ || \\ -C-OR_a \end{array}$, $\begin{array}{c} O \quad Ra \\ || \quad | \\ -C-N-Rb \end{array}$, $\begin{array}{c} O \\ || \\ -S-Ra \end{array}$, $\begin{array}{c} O \quad O \\ || \quad || \\ -S-Ra \end{array}$, $-SR_a$, and $\begin{array}{c} O \quad O \\ || \quad || \\ -S-NHR_a \end{array}$; provided R_a is not H in $\begin{array}{c} O \\ || \\ -S-Ra \end{array}$, $\begin{array}{c} O \quad O \\ || \quad || \\ -S-Ra \end{array}$, or $\begin{array}{c} R_b \quad O \\ | \quad || \\ -N-C-OR_a \end{array}$; or when R_1 and R_2 are on adjacent carbons on a ring, they can form

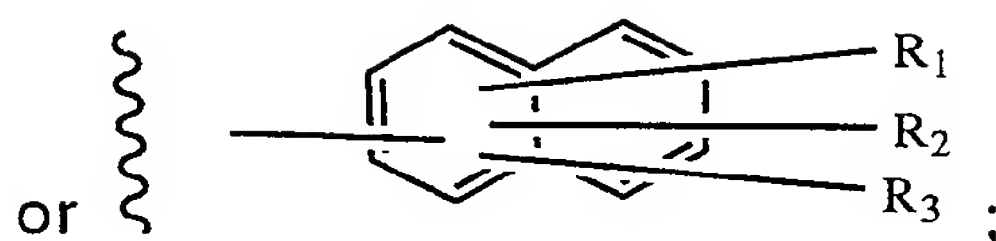
15  wherein n' is 1 or 2;

each R_3 is independently selected from the group consisting of H, C_1 - C_6 alkyl, $-CF_3$, $-C_2F_5$, $\begin{array}{c} O \\ || \\ -C-Ra \end{array}$, $-O-\begin{array}{c} O \\ || \\ -C-Ra \end{array}$, $\begin{array}{c} O \quad Ra \\ || \quad | \\ -C-N-Rb \end{array}$, Cl, Br, I, F, $-OR_a$, $-OCF_3$ or phenyl;

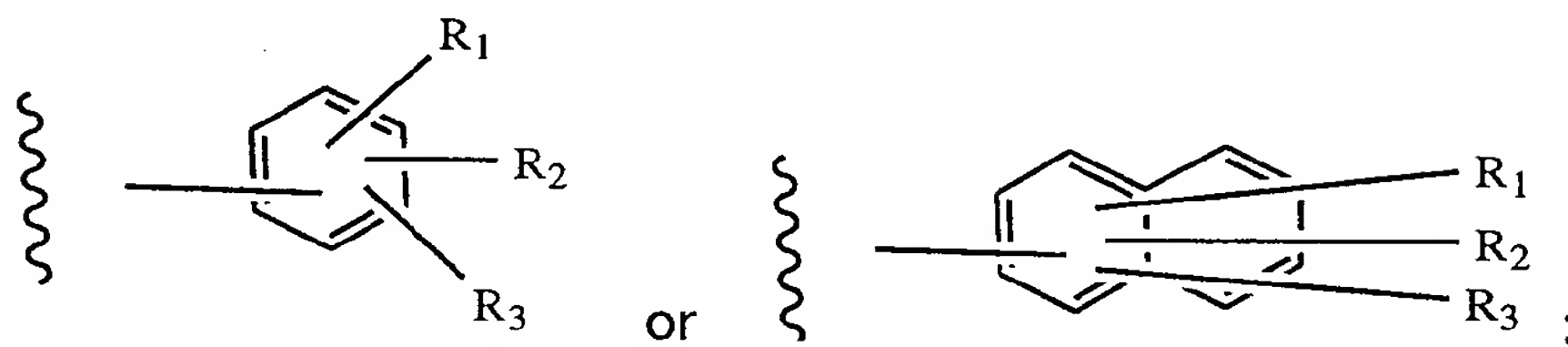
Ar_1 is heteroaryl or substituted heteroaryl,



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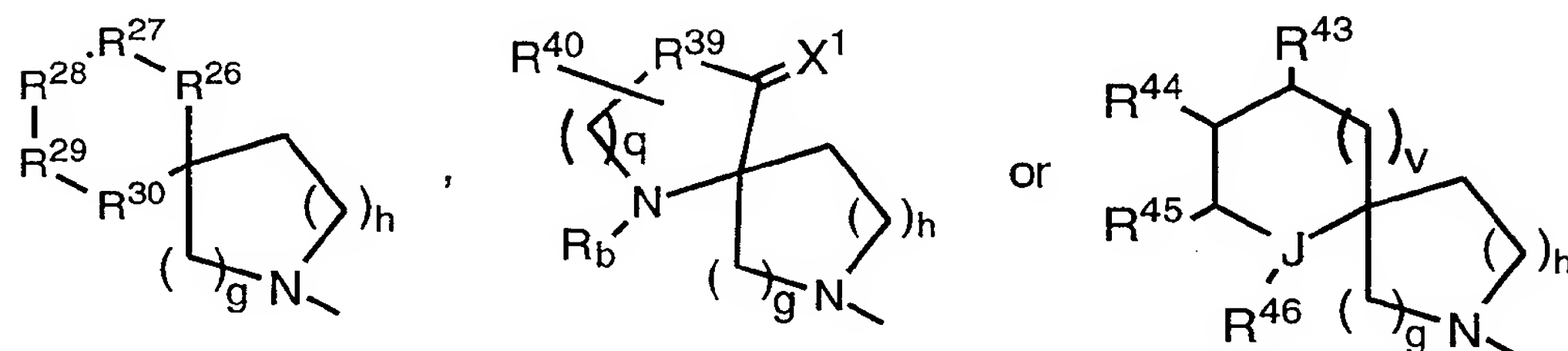


Q is =N- or =CH-;

Ar₂ is heteroaryl, substituted heteroaryl,

5

Z is



wherein the nitrogen in the unsubstituted ring is optionally quaternized with C₁₋₄ alkyl or phenyl-C₁₋₄ alkyl or is optionally present as the Noxide (N⁺O⁻);

10 g and h are each independently 0, 1, 2, 3, 4, or 5, with the proviso that g + h is equal to 1, 2, 3, 4, or 5;

v is 0, 1 or 2;

R²⁶ is selected from the group consisting of

- (1) a covalent bond
- 15 (2) C₁₋₃ alkylene, unsubstituted or substituted with a substituent selected from the group consisting of =O, -OH, -OR³⁵, halogeno, -CF₃, phenyl or mono, di or trisubstituted phenyl, wherein the substituents on the phenyl are independently selected from -OH, -CN, halogeno and -CF₃,
- 20 (3) S(O)_k
- (4) (C₁₋₃ alkylene)-S(O)_k
- (5) S(O)_k-(C₁₋₂ alkylene)
- (6) S(O)_kNH
- (7) S(O)_j-NR³⁵
- 25 (8) S(O)_j-NR³⁵-(C₁₋₂ alkylene)
- (9) CONH

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(10) $\text{CONR}^{35}\text{-(C}_{1-2}\text{ alkylene)}$ (11) CO_2 and(12) $\text{CO}_2\text{-(C}_{1-2}\text{ alkylene)}$

wherein j is 1 or 2 and k is 0, 1 or 2;

5 R^{27} is $\text{-NR}^{37}\text{-}$, -O- , -S- , -S(O)- , or $\text{-SO}_2\text{-}$, with the proviso that when R^{26} is a covalent bond and R^{28} is C_{1-3} alkyl, R^{27} must be NR^{37} ;

 R^{37} is selected from a group consisting of:

(1) H,

10 (2) $\text{C}_1\text{-}_8$ linear or branched alkyl, unsubstituted, monosubstituted or multiply substituted with -OR^{35} , =O , -NHCOR^{35} , $\text{-NR}^{35}\text{R}^{36}$, -CN , -halogeno , -CF_3 , -phenyl or substituted phenyl, wherein the substituents on phenyl are selected from the group consisting of -OH , -CN , halogeno and -CF_3 ;

15 (3) S(O)R^{38} , wherein R^{38} is C_{1-6} linear or branched alkyl, unsubstituted, mono di or trisubstituted with a substituent selected from the group consisting of =O , -CN , -OR^{35} , $\text{-NR}^{35}\text{R}^{36}$, $\text{-NR}^{36}\text{OR}^{36}$, -halogeno , -CF_3 , -phenyl or mono, di or trisubstituted phenyl, wherein the substituents on the phenyl are independently selected from the group consisting of -OH , =O , -CN , $\text{-NR}^{35}\text{R}^{36}$, $\text{-NR}^{35}\text{COR}^{36}$, -halogeno , -CF_3 and C_{1-3} alkyl;

(4) SO_2R^{38} ,(5) COR^{38} ,(6) CO_2R^{38} ;(7) $\text{CONR}^{36}\text{R}^{38}$;

25 R^{28} is selected from the group consisting of

(1) a covalent bond

(2) $\text{C}_1\text{-}_3$ alkylene, unsubstituted or substituted with a substituent selected from the group consisting of =O , -OR^{35} , halogeno , -CF_3 , phenyl or mono, di or trisubstituted phenyl, wherein the substituents on the phenyl are independently selected from the group consisting of -OR^{35} , halogeno and -CF_3 ;

(3) S(O)_k (4) $\text{(C}_{1-3}\text{ alkylene)-S(O)}_k$ (5) $\text{S(O)}_k\text{-(C}_{1-2}\text{ alkylene)}$

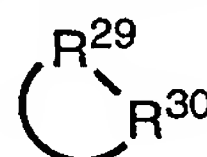
35 (6) NHS(O)_j

(7) $\text{NH(C}_{1-2}\text{ alkylene)-S(O)}_j$

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- (8) $S(O)_jNR^{35}$
- (9) $S(O)_j-NR^{35}-(C_{1-2} \text{ alkylene})$
- (10) $NHCO-(C_{1-2} \text{ alkylene})$
- (11) $NR^{35}CO$
- (12) $NR^{35}-(C_{1-2} \text{ alkylene})-CO$
- (13) $O(CO)$ and
- (14) $(C_{1-2} \text{ alkyl})O(CO)$;

R^{29} - R^{30} considered together are 2 adjoining atoms of the ring



10 said ring being a phenyl, naphthyl or heteroaryl group, and wherein the phenyl, naphthyl or heteroaryl group is unsubstituted, mono, di or tri substituted, wherein heteroaryl is selected from the group consisting of benzimidazolyl, benzofuranyl, benzoxazolyl, furanyl, imidazolyl, indolyl, isoxazolyl, isothiazolyl, oxadiazolyl, oxazolyl, 15 pyrazinyl, pyrazolyl, pyridyl, pyrimidyl, pyrrolyl, quinolyl, tetrazolyl, thiadiazolyl, thiazolyl, thienyl and triazolyl; and wherein the substituents are independently selected from the group consisting of:

(a) C_{1-6} alkyl, branched or unbranched, unsubstituted or mono or disubstituted by hydroxy

- (b) $=O$
- (c) OR^{35}
- (d) halogeno
- (e) CF_3
- (f) NO_2
- (g) CN
- (h) $NR^{35}R^{36}$
- (i) $NR^{35}COR^{36}$
- (j) $NR^{35}CO_2R^{36}$
- (k) $NR^{35}S(O)_jR^{36}$
- (l) $CONR^{35}R^{36}$
- (m) COR^{35}
- (n) CO_2R^{35}
- (o) $S(O)_jR^{35}$
- (p) heteroaryl, or mono or di substituted heteroaryl,

35 wherein heteroaryl is as defined above and the substituents are

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selected from the group consisting of: C₁₋₆ alkyl, branched or unbranched, unsubstituted or mono or disubstituted by OH; =O; OR³⁵; CF₃; -NO₂; CN; NR³⁵R³⁶; NR³⁵COR³⁶; NR³⁵CO₂R³⁶; NR³⁵S(O)_jR³⁶; CONR³⁵R³⁶; COR³⁵; CO₂R³⁵; S(O)_jR³⁵; and phenyl;

5 R³⁵ and R³⁶ are independently selected from:

(a) H,

(b) C₁₋₆ alkyl, or mono or disubstituted C₁₋₆ alkyl, wherein the substituents independently selected from the group consisting of phenyl, unsubstituted or substituted with -OH, C₁₋₃ alkyl, -CN, halogeno, -CF₃ or C₁₋₄ alkoxy; -OH; =O; -CN; halogeno; or -CF₃;

(c) phenyl, pyridinyl or thiophene, or mono, di or trisubstituted phenyl, pyridinyl or thiophene, wherein the substituents are independently selected from the group consisting of -OH, C₁₋₄ alkyl, -CN, halogeno and -CF₃;

15 (d) C₁₋₃ alkyloxy,

or

R³⁵ and R³⁶ are joined together to form a 5-, 6-, or 7-membered monocyclic saturated ring containing 1 or 2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and in which the ring is unsubstituted or mono or disubstituted, wherein the substituents are independently selected from the group consisting of -OH, =O, -CN, halogeno and -CF₃;

q is 1 or 2;

X¹ is =O or =S;

25 R³⁹ is -NR_b- or -CH₂-;

R⁴⁰ is H, C_{1-C6} alkyl, =O, phenyl, substituted phenyl, benzyl, substituted benzyl or allyl

J is carbon and R⁴³, R⁴⁴, R⁴⁵ and R⁴⁶ are independently selected from the group consisting of H, -OH, =O, -NR⁴⁷R⁴⁸ or -NR⁴⁷C(O)-NR^{47'}R⁴⁸, wherein the nitrogen of -NR⁴⁷R⁴⁸ is optionally quaternized with C₁₋₄ alkyl or phenyl-C₁₋₄ alkyl or is optionally present as the N-oxide; or R⁴³ and R⁴⁴, or R⁴⁴ and R⁴⁵, together form a carbon-carbon bond; or R⁴³ and R⁴⁴ or R⁴⁴ and R⁴⁵, or R⁴⁵ and R⁴⁶, together with the carbons to which they are attached form an aryl or heteroaryl ring, wherein heteroaryl is as defined above, and wherein the aryl or

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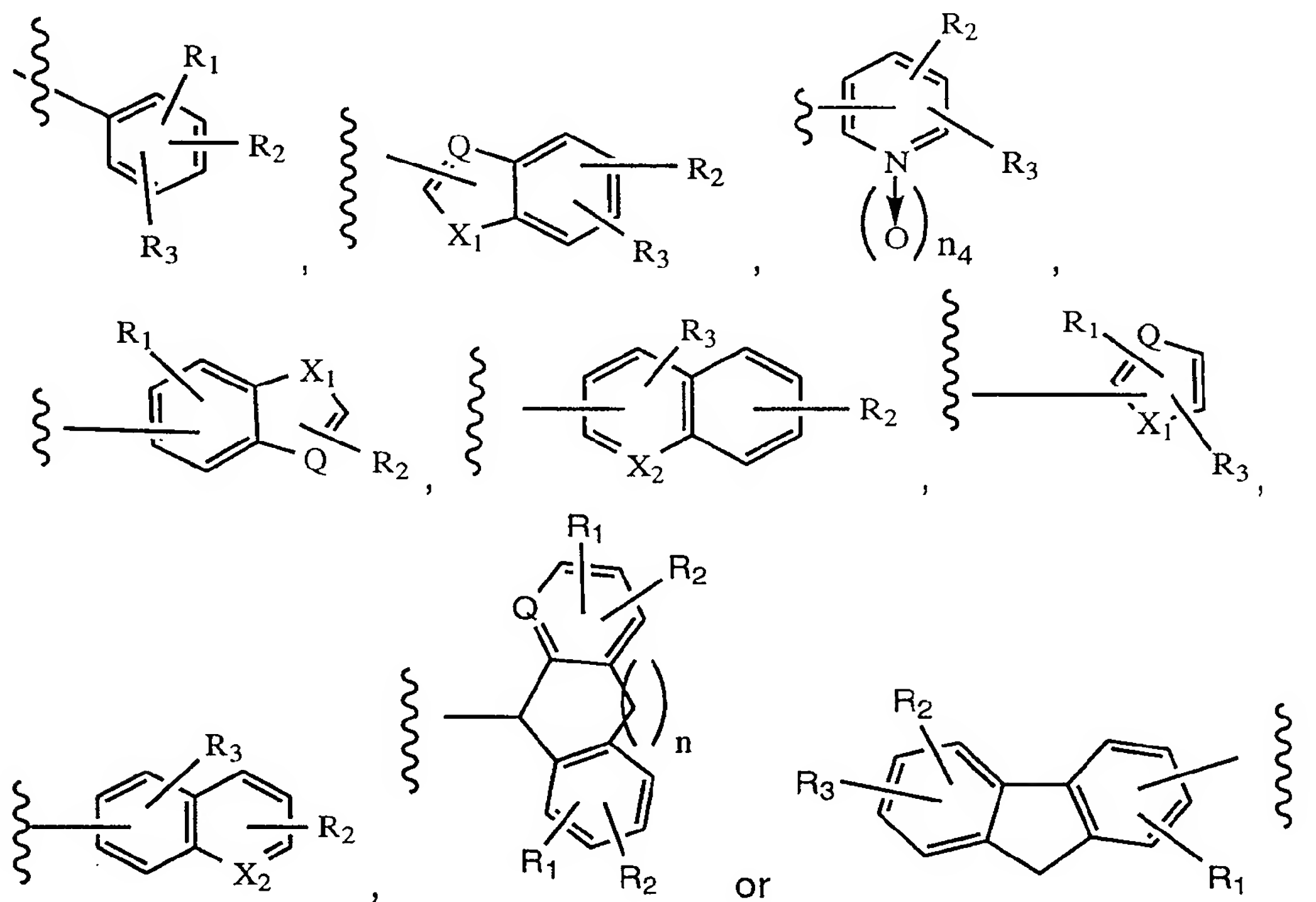
heteroaryl group is unsubstituted, mono, di or tri substituted, wherein the substituents are independently selected from the group consisting of:

- (a) C₁₋₆ alkyl, branched or unbranched, unsubstituted or mono or disubstituted by hydroxy
- 5 (b) =O
- (c) OR⁴⁷
- (d) halogeno
- (e) CF₃
- (f) NO₂
- 10 (g) CN
- (h) NR⁴⁷R⁴⁸
- (i) NR⁴⁷COR⁴⁸
- (j) NR⁴⁷CO₂R⁴⁸
- (k) NR⁴⁷S(O)_jR⁴⁸
- 15 (l) CONR⁴⁷R⁴⁸
- (m) COR⁴⁷
- (n) CO₂R⁴⁷
- (o) S(O)_kR⁴⁷
- (p) heteroaryl, or mono or di substituted heteroaryl,
- 20 wherein heteroaryl is as defined above and the substituents are selected from the group consisting of: C₁₋₆ alkyl, branched or unbranched, unsubstituted or mono or disubstituted by OH; =O; OR⁴⁷; CF₃; -NO₂; CN; NR⁴⁷R⁴⁸; NR⁴⁷COR⁴⁸; NR⁴⁷CO₂R⁴⁸; NR⁴⁷S(O)_jR⁴⁸; CONR⁴⁷R⁴⁸; COR⁴⁷; CO₂R⁴⁷; S(O)_jR⁴⁷; and phenyl;
- 25 or R⁴³, R⁴⁴ and R⁴⁵ are as defined above and J-R⁴⁶ is oxygen or S(O)_i, wherein i is 0, 1, or 2; and R⁴⁷, R^{47'} and R⁴⁸ are independently selected from the group consisting of:
- (a) H,
- 30 (b) C₁₋₆ alkyl, or mono or disubstituted C₁₋₆ alkyl, wherein the substituents independently selected from the group consisting of phenyl, -OH, =O, -CN, halogeno and -CF₃;
- (c) phenyl, naphthyl, or mono, di or trisubstituted phenyl or naphthyl, wherein the substituents are independently selected from the group consisting of -OH, C₁₋₃ alkyl, -CN, halogeno and -CF₃; and
- 35 (d) C₁₋₃ alkyloxy; or

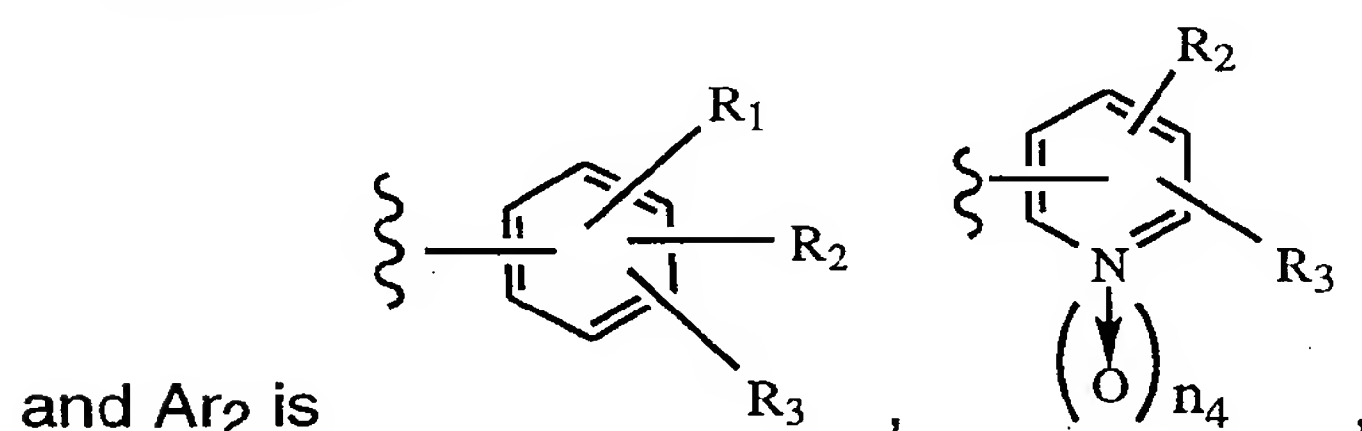
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- 5 R^{47} and R^{48} are joined together to form a 5-, 6-, or 7-membered monocyclic saturated ring containing 1 or 2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and in which the ring is unsubstituted or mono or disubstituted, wherein the substituents are independently selected from the group consisting of -OH, =O, -CN, halogeno and -CF₃;
 or an enantiomer or diastereomer thereof,
 or a pharmaceutically acceptable salt thereof.

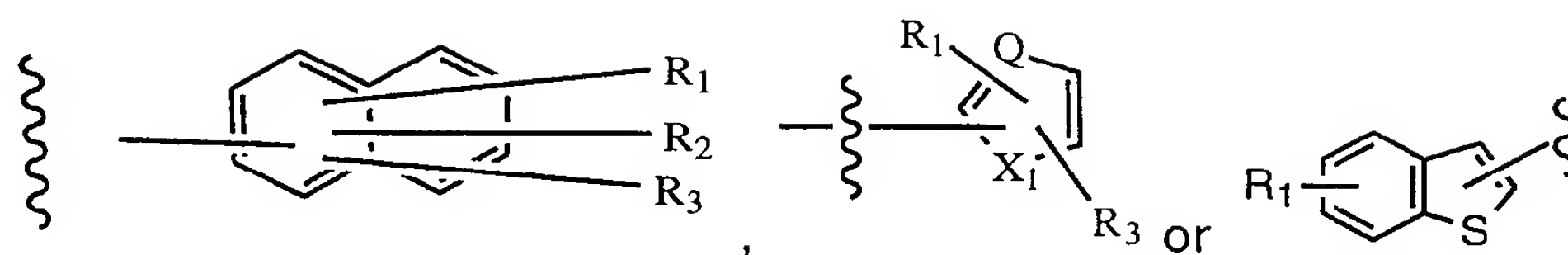
- 10 2. A compound according to claim 1, wherein m is 1; each X is =O; l is 0; n is 1; u is 0; and y is 1 to 3; Ar₁ is



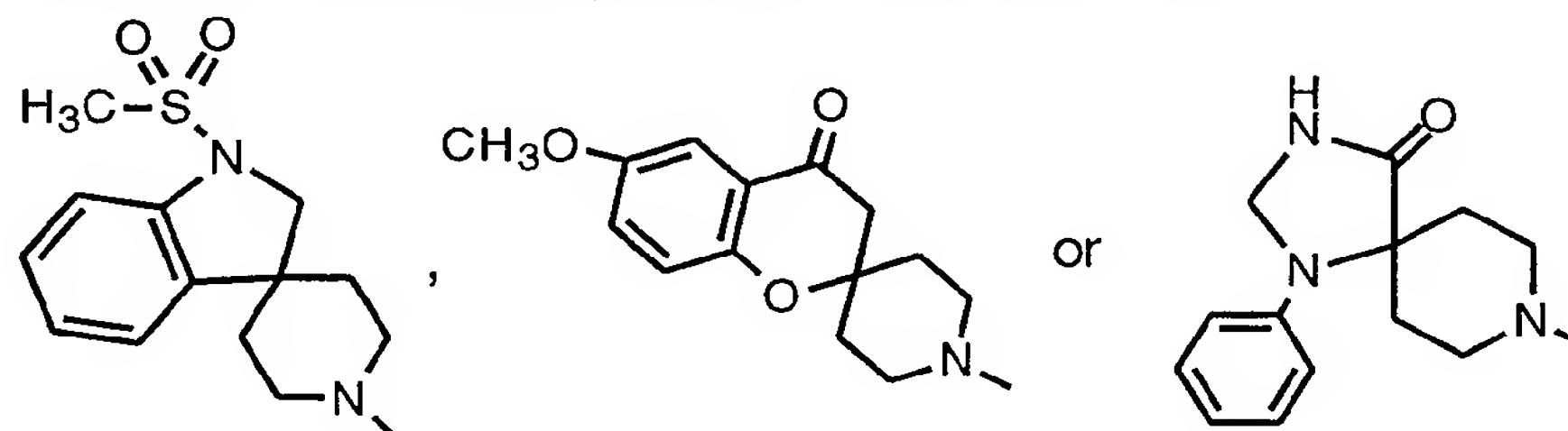
- 15 wherein Q is =N- or =CH-;
 each X₁ is independently -O-, -S- or -NR_a-;
 each X₂ is independently =CH- or -N=;
 n₄ is 0 or 1;



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3. A compound according to claim 2 wherein Z is



5

4. A compound according to claim 1 selected from the group consisting of:

2-(3,4-dichlorophenyl)-4-(3,5-dimethylbenzoyl)-1-[1,2-dihydro-1-(methanesulfonyl)spiro[3H-indole-3,4'-piperidine]-1'-yl]-1-oxopropyl]-piperazine;

10

2-(3,4-dichlorophenyl)-1-[3-[3,4-dihydro-4-oxo-6-methoxy-spiro[2H-1-benzopyran-2,4'-piperidin]-1'-yl]-1-oxopropyl]-4-(3,5-dimethyl-benzoyl)piperazine; and

15

2-(3,4-dichlorophenyl)-4-(3,5-dimethylbenzoyl)-1-[3-1-phenyl-4-oxo-1,3,8-triazaspiro[4.5]decan-8-yl]-1-oxopropyl]piperazine.

5. A composition comprising a neurokinin antagonistic effective amount of a compound according to claim 1 and a pharmaceutically acceptable carrier material.

20

6. A method for inducing neurokinin antagonism which comprises administering a neurokinin antagonistic effective amount of a compound according to claim 1 to a mammal in need thereof.

25

7. A method for treating chronic airway diseases such as asthma and allergies; inflammatory diseases such as inflammatory bowel disease, psoriasis, fibrositis, osteoarthritis, and rheumatoid arthritis; migraine; central nervous system disorders such as depression, emesis, psychosis, dementia, and Alzheimer's disease; Down's syndrome;

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neuropathy; multiple sclerosis; ophthalmic disorders; conjunctivitis; auto
immune disorders; graft rejection; systemic lupus erythematosus; GI
disorders such as Crohn's disease and ulcerative colitis; disorders of
bladder function; circulatory disorders such as angina; Raynaud's
5 disease; coughing and pain, which comprises administering a
therapeutically effective amount of a compound according to claim 1.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 97/22519

A. CLASSIFICATION OF SUBJECT MATTER IPC 6 C07D471/10 C07D491/10 A61K31/445 //(C07D471/10,221:00, 209:00),(C07D471/10,235:00,221:00),(C07D491/10,311:00,221:00)		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 6 C07D		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 96 34864 A (SCHERING CORP.) 7 November 1996 cited in the application see claims 1,21,22 ---	1,2,5
Y	WO 94 29309 A (MERCK & CO., INC.) 22 December 1994 cited in the application see page 39, line 17 - line 22; claims 1-5,7,15,16 ---	1-3,5
Y	WO 94 17045 A (MERCK & CO., INC.) 4 August 1994 cited in the application see page 22, line 27 - line 31; claims 1-5,11,13,14 ---	1-3,5
-/-		
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.		
° Special categories of cited documents : <div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div>		
Date of the actual completion of the international search <div style="text-align: center; font-size: 1.2em;">17 April 1998</div>		Date of mailing of the international search report <div style="text-align: center; font-size: 1.2em;">27.04.98</div>
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer <div style="text-align: center; font-size: 1.2em;">Hass, C</div>

INTERNATIONAL SEARCH REPORT

Intern: al Application No
PCT/US 97/22519

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,P	WO 97 22597 A (FUJISAWA PHARMACEUTICAL CO., LTD.) 26 June 1997 see page 1, line 8 - line 21; claims 1,10,13,14 ---	1,5
A	EP 0 533 244 A (MERCK & CO. INC.) 24 March 1993 see page 59 - page 70; claim 1; examples -----	1

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 97/22519

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 6 and 7
are directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 97/22519

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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